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March 16, 1992

#32

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re : U.S. Patent No. 4,761,418

Issued : August 2, 1988

To : Roy A. Swaringen, Jr., Hassan A. El-Sayad, David A. Yeowell, John A. Savarese

For : NOVEL COMPOUNDS

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, DC 20231

Re: Deposit Account: 02-4857
BURROUGHS WELLCOME CO.
U.S. Patent No. 4,761,418

Sir:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM under 35 U.S.C. 156 with regard to U.S. Patent No. 4,761,418.

Applicant's check of $1,000.00 is forwarded herewith to cover the application fee. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit overpayment to Account No. 02-4857. Triplicate copies of this sheet are enclosed.

Respectfully submitted,

By: _____
Lawrence A. Nielsen (Reg. No. 29682)
Head, Patent Department
Burroughs Wellcome Co.

Docket No. 92/PD/436
"Express Mail" label no. AB192630471
Date of Deposit March 16, 1992

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Box Patent Ext. Washington, DC 20231.

_____
Robert T. Hrubiec

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RH/rc*

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March 16, 1992

Commissioner of Patents and Trademarks
Box Patent Ext.
Washington, DC 20231

Sir:

Please address all communications relating to the enclosed APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156 of U.S. Patent No. 4,761,418 to Dr. L. A. Nielsen, Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, NC 27709; telephone no. (919) 248-4126.

Very truly yours,

David A. Yeowell

David A. Yeowell, Ph.D.
Vice President - Technical Development

DAY/rc*

Docket No. 92/PD/436

"Express Mail" label no. AB192630471

Date of Deposit March 16, 1992

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Robert T. Hrubiec

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 4,761,418

Issued: August 2, 1988

To: Roy A. Swaringen, Jr.; Hassan A. El-Sayad; David A. Yeowell; John A. Savarese

For: NOVEL COMPOUNDS

Commissioner of Patents and Trademarks

Box Patent Ext.

Washington, D.C. 20231

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

Sir:

Applicant, BURROUGHS WELLCOME CO., a corporation of the State of North Carolina, represents that it is the co-assignee with General Hospital Corporation of the entire interest in and to Letters Patent of the United States of America No. 4,761,418 granted to

Roy A. Swaringen, Jr.; Hassan A. El-Sayad; David A. Yeowell; and John A. Savarese on August 2, 1988 for NOVEL COMPOUNDS by virtue of assignments to BURROUGHS WELLCOME CO. recorded in the United States Patent and Trademark Office on August 24, 1987, Reel 4749, Frames 0941 and 0945 and by virtue of an assignment to General Hospital Corporation recorded in the United States Patent and Trademark Office on April 4, 1988, Reel 4847, Frames 0327-0328.

Applicant hereby submits this application for extension of patent term under 35 U.S.C. 156 by providing the following information pursuant to 37 CFR 1.740. For convenience, the information contained in this application will be presented according to the format set forth in 37 CFR 1.740.

(1) This application for extension is based upon the regulatory review period before the Food and Drug Administration ("FDA") of Applicant's approved product, MIVACRON® Injection (mivacurium chloride), hereinafter "MIVACRON® Injection". The only active ingredient in MIVACRON® Injection is mivacurium chloride. A copy of the package insert approved by FDA as part of NDA 20-098 (described below) for the approved product is attached hereto.

Mivacurium chloride is designated chemically as [R-[R*, R*-(E)]]-2,2'-[(1,8-dioxo-4-octene-1,8-diyl)bis(oxy-3,1-propanediyl)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]isoquinolinium] dichloride. The molecular formula is $C_{58}H_{80}Cl_2N_2O_{14}$ and the molecular weight is 1100.18.

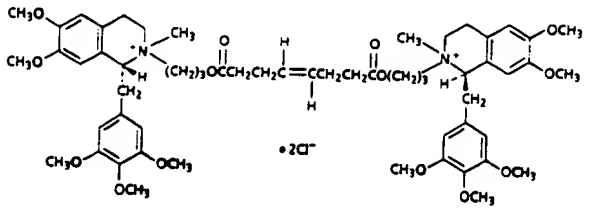
Mivacurium chloride is a mixture of three stereoisomers:

a) (1R, 1'R, 2S, 2'S), the *trans-trans* diester;

b) (1R, 1'R, 2R, 2'S), the *cis-trans* diester; and

c) (1R, 1'R, 2R, 2'R), the *cis-cis* diester.

The *trans-trans* and *cis-trans* stereoisomers comprise 92% to 96% of mivacurium chloride and their neuromuscular blocking potencies are not significantly different from each other or from mivacurium chloride. The *cis-cis* diester has been estimated from studies in cats to have one-tenth the neuromuscular blocking potency of the other two stereoisomers. The structural formula of mivacurium chloride is:



Mivacurium chloride is also known as (E)-(1R, 1'R)-2,2'-[4-octenedioylbis-(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride, and this alternative nomenclature is used in U.S. Patent 4,761,418.

The individual stereoisomers comprising mivacurium chloride and claimed in U.S. Patent 4,761,418 are:

a) (E)-(1R, 1'R, 2S, 2'S)-2,2'-[4-octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride, the *trans-trans* diester;

b) (E)-(1R, 1'R, 2R, 2'S)-2,2'-[4-octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride, *cis-trans* diester; and

c) (E)-(1R, 1'R, 2R, 2'R,)-2-2'-[4-octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl) isoquinolinium]dichloride, the *cis-cis* diester.

(2) The approved product, MIVACRON® Injection, was subject to regulatory review under Federal Food, Drug and Cosmetic Act, Section 505 (21 U.S.C. 355).

(3) MIVACRON® Injection received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on January 22, 1992.

(4) Mivacurium chloride, the only active ingredient in MIVACRON® Injection, has not been previously approved for commercial marketing under the Federal Food Drug and Cosmetic Act. Furthermore, the constituent stereoisomers of mivacurium chloride, as described hereinbefore, either individually or in any combination have not been previously approved for commercial marketing under the Federal Food Drug and Cosmetic Act.

(5) This application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60 day period, which period will expire on March 22, 1992.

(6) The complete identification of the patent for which extension of term is being sought is as follows:

Inventors: Roy A. Swaringen, Jr.; Hassan A. El-Sayad;

David A. Yeowell; John J. Savarese

Patent Number: 4,761,418

Issue Date: August 2, 1988

Expiration Date: August 2, 2005

(7) A complete copy of the patent identified in paragraph (6) above is appended hereto as EXHIBIT 1.

(8) No disclaimer, certificate of correction, receipt of maintenance fee payment or reexamination certificate exists in respect of U.S. Patent 4,761,418.

(9) United States Patent Number 4,761,418 claims the approved product MIVACRON® Injection, a method of using the approved product MIVACRON® Injection, and a pharmaceutical composition comprising the approved product MIVACRON® Injection. The patent claims applicable to the approved product are as follows:

Claim 1 reads as follows:

1. 2,2'-[(E)-4-Octenedioylbis(oxytrimethylene)]bis[(trans)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] cation in association with a pharmaceutically acceptable anion.

The active ingredient of the approved product is mivacurium chloride which is a mixture of stereoisomers comprising one of the isomers of the compound of claim 1 wherein the anion is chloride.

Claim 2 reads as follows:

2. 2,2'-[(E)-4-Octenedioylbis(oxytrimethylene)]bis[(trans)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride.

The active ingredient of the approved product is mivacurium chloride which is a mixture of the stereoisomers comprising one of the isomers of the compound of claim 2.

Claim 5 reads as follows:

5. (E)-(1R, 1'R)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium) cation in association with a pharmaceutically acceptable anion.

The active ingredient of the approved product is mivacurium chloride which is a mixture of stereoisomers comprising the compound of claim 5 wherein the anion is chloride.

Claim 6 reads as follows:

6. (E)-(1R,1'R)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis(1,2,4,3-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride.

The active ingredient of the approved product is mivacurium chloride which is a mixture of stereoisomers comprising the compound of Claim 6.

Claim 7 reads as follows:

7. (E)-(1R,1'R, 2R, 2'R)-2-2'-[4-Octenedioylbis[oxytrimethylene)]bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]cation in association with a pharmaceutically acceptable anion.

The active ingredient of the approved product is mivacurium chloride which (a) is a mixture of stereoisomers and (b) comprises, as one of the stereoisomers, the compound of claim 7 wherein the anion is chloride.

Claim 8 reads as follows:

8. (E)-(1R, 1'R, 2R, 2'R)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride.

The active ingredient of the approved product is mivacurium chloride which (a) is a mixture of stereoisomers and (b) comprises, as one of the stereoisomers, the compound of claim 8.

Claim 9 reads as follows:

9. (E)-(1R, 1'R, 2R, 2'S)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] cation in association with a pharmaceutically acceptable anion.

The active ingredient of the approved product is mivacurium chloride which (a) is a mixture of stereoisomers and (b) comprises, as one of the stereoisomers, the compound of claim 9 wherein the anion is chloride.

Claim 10 reads as follows:

10. (E)-(1R, 1'R, 2R, 2'S)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]chloride.

The active ingredient of the approved product is mivacurium chloride which (a) is a mixture of stereoisomers and (b) comprises, as one of the stereoisomers, the compound of claim 10.

Claim 11 reads as follows:

11. (E)-(1R, 1'R, 2S, 2'S)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dication in association with a pharmaceutically acceptable anion.

The active ingredient of the approved product is mivacurium chloride which (a) is a mixture of stereoisomers and (b) comprises, as one of the stereoisomers, the compound of Claim 11 wherein the anion is chloride.

Claim 12 reads as follows:

12. (E)-(1R, 1'R, 2S, 2'S)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride.

The active ingredient of the approved product is mivacurium chloride which (a) is a mixture of stereoisomers and (b) comprises, as one of the stereoisomers, the compound of claim 12.

13. A method for producing muscle relaxation in a mammal which comprises parenterally administering to a mammal an effective muscle relaxant amount of the compound of claim 1, 3 or 5.

The approved product is indicated for producing muscle relaxation in humans by intravenous administration and contains the active ingredient mivacurium chloride which (a) is a mixture of stereoisomers and (b) comprises compounds of claim 1 or 5 wherein the anion is chloride.

14. A sterile pharmaceutical composition comprising one or more of the compounds of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 in an effective muscle relaxant amount and a pharmaceutically acceptable solvent therefor.

The approved product is a sterile, non-pyrogenic aqueous solution containing the active ingredient mivacurium chloride which is a mixture of stereoisomers comprising compounds of claims 1, 5, 7, 9, or 11, wherein the anion is chloride or compounds of claims 2, 6, 8, 10 or 12 *per se*; in the pharmaceutically acceptable solvent Water for Injection or 5% Dextrose Injection USP. The approved product in Water for Injection contains 0.9% w/v benzylalcohol and hydrochloric acid may be added to adjust the pH to 3.5-5.0.

15. A method for producing muscle relaxation in a mammal which comprises parenterally administering to a mammal an effective muscle relaxant amount of one or more of the compounds of claims 9, 10, 11 or 12.

The approved product is indicated for producing muscle relaxation in humans by intravenous administration and contains the active ingredient mivacurium chloride which (a) is a mixture of stereoisomers and (b) comprises the compounds of claims 9 and 11 wherein the anion is chloride or the compounds of claims 10 and 12 *per se*.

(10) The relevant dates and information pursuant to 35 U.S.C. 156(g) necessary to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) Investigational New Drug application ("IND") for MIVACRON® Injection was filed June 7, 1984 as IND 24,310 and became effective on July 7, 1984;

(b) U.S. Patent No. 4,761,418 was issued August 2, 1988;

(c) New Drug Application ("NDA") for MIVACRON® Injection was submitted August 30, 1990 as NDA 20-098;

(d) NDA 20-098 for MIVACRON® Injection was approved by the FDA on January 22, 1992.

(11) As a brief description of the activities undertaken by the Applicant during the applicable regulatory review period, attached hereto as EXHIBIT 2, is a chronology of the major communications between the Applicant and the FDA from June 7, 1984 to January 22, 1992.

(12) Applicant is of the opinion that U.S. Patent 4,761,418 is eligible for extension under 35 U.S.C. 156 because it satisfies all the requirements for such extensions as follows:

(a) 35 U.S.C. 156 (a)

U.S. Patent 4,761,418 claims a product and a method of using a product.

(b) 35 U.S.C. 156(a)(1)

The term of U.S. Patent 4,761,418 has not expired before submission of this application.

(c) 35 U.S.C. 156 (a)(2)

The term of U.S. Patent 4,761,418 has never been extended.

(d) 35 U.S.C. 156 (a)(3)

The application for extension is submitted by one of the owners of record through its agent on behalf of itself and on behalf of the other owner of record in accordance with the requirements of 35 U.S.C. 156(d) and 37 CFR 1.710 *et. seq.*

(e) 35 U.S.C. 156 (a)(4)

The approved product, MIVACRON® Injection, has been subject to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. 156 (a)(5)(A)

The commercial marketing or use of the approved product, MIVACRON® Injection, after the regulatory review period is the first permitted commercial marketing or use of the approved product under the provisions of the Federal Food, Drug, and Cosmetic Act (21 USC 355) under which such regulatory review period occurred.

The length of the extension of the patent term of U.S. Patent 4,761,418 claimed by applicant is 172 days which extends the term of U.S. Patent 4,761,418 from August 2, 2005 to January 22, 2006. This term is less than the sum of; (A) one half of that portion of the regulatory review period for the approved product occurring after the date of issuance of U.S. Patent 4,761,418 (i.e., August 2, 1988) and ending on the date NDA 20-098 for the approved product was submitted (i.e., August 30, 1990) and (B) that portion of the regulatory review period commencing on the date NDA 20-098 for the approved product was submitted (i.e., August 30, 1990) and ending on the date NDA 20-098 was approved (i.e., January 22, 1992), such sum being equal to 889 days. The extension of the term of U.S. Patent 4,761,418 by 889 days would result in the extended term being greater than 14 years from the date of approval of the approved product. Therefore, the extension term is reduced to 172 days in accordance with 35 USC 156(c)(3).

(13) The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension.

Attached hereto is a Declaration signed on behalf of the Applicant which meets the criteria set forth in 37 CFR 1.740 (17).

A check for $1,000.00 payable to the Commissioner of Patents and Trademarks is attached to cover the fee for this application for extension of term. In the event the actual fee differs from that specified above, it is requested that the overpayment be charged or the underpayment credited as authorized in the attached letter from Lawrence A. Nielsen.

Respectfully submitted,
Burroughs Wellcome Co.

by David A. Yeowell
David A. Yeowell
Vice President - Technical Development

CERTIFICATION

The undersigned hereby certifies that this Application For Extension of Patent Term Under 35 U.S.C. 156 including its EXHIBITS and supporting papers is being submitted as duplicate originals.

March 16 1992
Date

David A. Yeowell
David A. Yeowell

RH/rc*/15 - USP 4,761,418

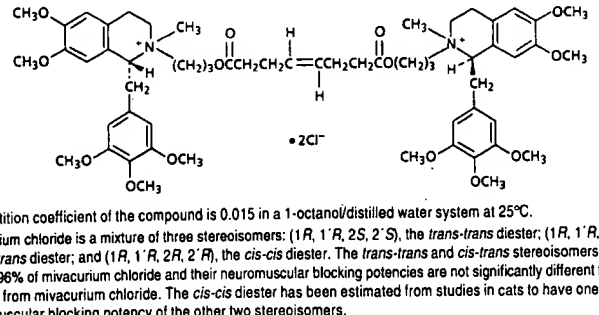
000028

MIVACRON® INJECTION
MIVACRON® PREMIXED INFUSION
(MIVACURIUM CHLORIDE)

Wellcome

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: MIVACRON (mivacurium chloride) is a short-acting, nondepolarizing skeletal muscle relaxant for intravenous administration. Mivacurium chloride is [*R*-[*R**,*R**-(*E*)]]-2,2'-[(1,8-dioxo-4-octene-1,8-diyl)bis(oxy-3,1-propanediyl)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]isoquinolinium] dichloride. The molecular formula is $C_{58}H_{80}Cl_2N_2O_{14}$ and the molecular weight is 1100.18. The structural formula is:



The partition coefficient of the compound is 0.015 in a 1-octanol/distilled water system at 25°C.

Mivacurium chloride is a mixture of three stereoisomers: (1*R*, 1'*R*, 2*S*, 2'*S*), the *trans-trans* diester; (1*R*, 1'*R*, 2*R*, 2'*S*), the *cis-trans* diester; and (1*R*, 1'*R*, 2*R*, 2'*R*), the *cis-cis* diester. The *trans-trans* and *cis-trans* stereoisomers comprise 92% to 96% of mivacurium chloride and their neuromuscular blocking potencies are not significantly different from each other or from mivacurium chloride. The *cis-cis* diester has been estimated from studies in cats to have one-tenth the neuromuscular blocking potency of the other two stereoisomers.

MIVACRON Injection is a sterile, non-pyrogenic solution (pH 3.5 to 5.0) containing mivacurium chloride equivalent to 2 mg/mL mivacurium in Water for Injection. Hydrochloric acid may have been added to adjust pH. Multiple dose vials contain 0.9% w/v benzyl alcohol. MIVACRON Premixed Infusion is a sterile, non-pyrogenic solution (pH 3.5 to 5.0; 260 mOsmol/L-measured) containing mivacurium chloride equivalent to 0.5 mg/mL mivacurium in 5% Dextrose Injection USP. Hydrochloric acid may have been added to adjust pH.

CLINICAL PHARMACOLOGY: MIVACRON (a mixture of three stereoisomers) binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a block of neuromuscular transmission. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine.

Pharmacodynamics: The time to maximum neuromuscular block is similar for recommended doses of MIVACRON and intermediate-acting agents (*e.g.*, atracurium), but longer than for the ultra-short-acting agent, succinylcholine. The clinically effective duration of action of the stereoisomers in MIVACRON (a mixture of three stereoisomers) is one-third to one-half that of intermediate-acting agents and 2 to 2.5 times that of succinylcholine.

The average ED_{95} (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of MIVACRON is 0.07 mg/kg (range: 0.06 to 0.09) in adults receiving opioid/nitrous oxide/oxygen anesthesia. The pharmacodynamics of doses of MIVACRON ≥ED_{95} administered over 5 to 15 seconds during opioid/nitrous oxide/oxygen anesthesia are summarized in Table 1. The mean time for spontaneous recovery of the twitch response from 25% to 75% of control amplitude is about 6 minutes (range: 3 to 9, n=32) following an initial dose of 0.15 mg/kg MIVACRON and 7 to 8 minutes (range: 4 to 24, n=85) following initial doses of 0.20 or 0.25 mg/kg MIVACRON.

Volatile anesthetics may decrease the dosing requirement for MIVACRON and prolong the duration of action; the magnitude of these effects may be increased as the concentration of the volatile agent is increased. Isoflurane and enflurane (administered with nitrous oxide/oxygen to achieve 1.25 MAC [Minimum Alveolar Concentration]) may decrease the effective dose of MIVACRON by as much as 25%, and may prolong the clinically effective duration of action and decrease the average infusion requirement by as much as 35% to 40%. At equivalent MAC values, halothane has little or no effect on the ED_{50} of MIVACRON, but may prolong the duration of action and decrease the average infusion requirement by as much as 20% (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY and **Drug Interaction** subsection of PRECAUTIONS).

Table 1
Pharmacodynamic Dose Response During Opioid/Nitrous Oxide/Oxygen Anesthesia

Initial MIVACRON Dose (mg/kg)		Time to Maximum Block[1] (min)	Time to Spontaneous Recovery[1] 5% Recovery (min)	25% Recovery[2] (min)	95% Recovery[3] (min)	T_4/T_1 Ratio ≥ 75%[3] (min)
Adults						
0.07 to 0.10	[n=47]	4.9 (2.0-7.6)	11 (7-19)	13 (8-24)	21 (10-36)	21 (10-36)
0.15	[n=50]	3.3 (1.5-8.8)	13 (6-31)	16 (9-38)	26 (16-41)	26 (15-45)
0.20	[n=50]	2.5 (1.2-6.0)	16 (10-29)	20 (10-36)	31 (15-51)	34 (19-56)
0.25	[n=48]	2.3 (1.0-4.8)	19 (11-29)	23 (14-38)	34 (22-64)	43 (26-75)
Children 2 to 12 Years						
0.11 to 0.12	[n=17]	2.8 (1.2-4.6)	5 (3-9)	7 (4-10)	–	–
0.20	[n=18]	1.9 (1.3-3.3)	7 (3-12)	10 (6-15)	19 (14-26)	16 (12-23)
0.25	[n=9]	1.6 (1.0-2.2)	7 (4-9)	9 (5-12)	–	–

[1]Values shown are medians of means from individual studies (range of individual patient values).
[2]Clinically effective duration of neuromuscular block.
[3]Data available for as few as 40% of adults in specific dose groups and for 22% of children in the 0.20 mg/kg dose group due to administration of reversal agents or additional doses of MIVACRON prior to 95% recovery or T_4/T_1 ratio recovery to ≥75%.

Administration of MIVACRON over 60 seconds does not alter the time to maximum neuromuscular block or the duration of action. The duration of action of the stereoisomers in MIVACRON may be prolonged in patients with reduced plasma cholinesterase (pseudocholinesterase) activity (see **Reduced Plasma Cholinesterase Activity** subsection of PRECAUTIONS and **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Interpatient variability in duration of action occurs with MIVACRON as with other neuromuscular blocking agents. However, analysis of data from 224 patients in clinical studies receiving various doses of MIVACRON during opioid/nitrous oxide/oxygen anesthesia with a variety of premedicants and varying lengths of surgery indicated that approximately 90% of the patients had clinically effective durations of block within 8 minutes of the median duration predicted from the dose-response data shown in Table 1. Variations in plasma cholinesterase activity, including values within the normal range and values as low as 20% below the lower limit of the normal range, were not associated with clinically significant effects on duration. The variability in duration, however, was greater in patients with plasma cholinesterase activity at or slightly below the lower limit of the normal range.

A dose of 0.15 mg/kg (2 x ED_{95}) MIVACRON administered during the induction of thiopental/opioid/nitrous oxide/oxygen anesthesia produced generally good-to-excellent conditions for tracheal intubation in 2.5 minutes. Doses of 0.20 and 0.25 mg/kg (3 and 3.5 x ED_{95}) yielded similar conditions in 2.0 minutes.

Repeated administration of maintenance doses or continuous infusion of MIVACRON for up to 2.5 hours is not associated with development of tachyphylaxis or cumulative neuromuscular blocking effects in ASA Physical Status I-II patients. Limited data are available from patients receiving infusions for longer than 2.5 hours. Spontaneous recovery of neuromuscular function after infusion is independent of the duration of infusion and comparable to recovery reported for single doses (Table 1).

The neuromuscular block produced by the stereoisomers in MIVACRON is readily antagonized by anticholinesterase agents. As seen with other nondepolarizing neuromuscular blocking agents, the more profound the neuromuscular block at the time of reversal, the longer the time and the greater the dose of anticholinesterase agent required for recovery of neuromuscular function.

In children (2 to 12 years), MIVACRON has a higher ED_{95} (0.10 mg/kg), faster onset, and shorter duration of action than in adults. The mean time for spontaneous recovery of the twitch response from 25% to 75% of control amplitude is about 5 minutes (n=4) following an initial dose of 0.20 mg/kg MIVACRON. Recovery following reversal is faster in children than in adults (Table 1).

Hemodynamics: Administration of MIVACRON in doses up to and including 0.15 mg/kg (2 x ED_{95}) over 5 to 15 seconds to ASA Physical Status I-II patients during opioid/nitrous oxide/oxygen anesthesia is associated with minimal change in mean arterial blood pressure (MAP) or heart rate (HR) (Table 2).

Table 2
Cardiovascular Dose Response During Opioid/Nitrous Oxide/Oxygen Anesthesia

Initial MIVACRON Dose (mg/kg)		% of Patients With ≥30% Change MAP Dec	MAP Inc	HR Dec	HR Inc
Adults					
0.07 to 0.10	[n=49]	0%	2%	0%	0%
0.15	[n=53]	4%	4%	4%	2%
0.20	[n=53]	30%	0%	0%	8%
0.25	[n=44]	39%	2%	0%	14%
Children 2 to 12 years					
0.11 to 0.12	[n=17]	0%	6%	0%	0%
0.20	[n=17]	0%	0%	0%	0%
0.25	[n=8]	13%	0%	0%	0%

Higher doses of ≥0.20 mg/kg (≥3 x ED_{95}) may be associated with transient decreases in MAP and increases in HR in some patients. These decreases in MAP are usually maximal within 1 to 3 minutes following the dose, typically resolving without treatment in an additional 1 to 3 minutes, and are usually associated with increases in plasma histamine concentration. Decreases in MAP can be minimized by administering MIVACRON over 30 or 60 seconds (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY and **General** subsection of PRECAUTIONS).

Analysis of 426 patients in clinical studies receiving initial doses of MIVACRON up to and including 0.30 mg/kg (*i.e.*, 2 times the recommended intubating dose) during opioid/nitrous oxide/oxygen anesthesia showed that high initial dose and a rapid rate of injection contributed to a greater probability of experiencing a decrease of ≥ 30% in MAP after MIVACRON administration. Obese patients also had a greater probability of experiencing a decrease of ≥30% in MAP when dosed on the basis of actual body weight, thereby receiving a larger dose than if dosed on the basis of ideal body weight (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY and the **General** subsection of PRECAUTIONS).

Children experience minimal changes in MAP or HR after administration of MIVACRON doses up to and including 0.25 mg/kg over 5 to 15 seconds, but higher doses (≥0.25 mg/kg) may be associated with transient decreases in MAP (Table 2).

Following a dose of 0.15 mg/kg MIVACRON administered over 60 seconds, adult patients with significant cardiovascular disease undergoing coronary artery bypass grafting or valve replacement procedures showed no clinically important changes in MAP or HR. Transient decreases in MAP were observed in some patients after doses of 0.20 or 0.25 mg/kg MIVACRON administered over 60 seconds. The number of patients in whom these decreases in MAP required treatment was small.

Pharmacokinetics: Table 3 describes the results from a study of 9 ASA Physical Status I-II adult patients (31 to 48 years) receiving an infusion of MIVACRON at 5 µg/kg/min for 60 minutes followed by 10 µg/kg/min for 60 minutes. MIVACRON is a mixture of isomers which do not interconvert *in vivo*. The mivacurium pharmacokinetic parameters presented in Table 3 were determined using a stereospecific assay. The two more potent isomers, *cis-trans* (36% of the mixture) and *trans-trans* (57% of the mixture), have very high clearances that exceed cardiac output reflecting the extensive metabolism by plasma cholinesterase. The volume of distribution is relatively small, reflecting limited tissue distribution secondary to the polarity and large molecular weight of mivacurium. The combination of high metabolic clearance and low distribution volume results in the short elimination half-life of approximately 2 minutes for the two active isomers. The short elimination half-lives and high metabolic clearances of the active isomers are consistent with the short duration of action of MIVACRON. The steady-state concentrations of the *cis-trans* and *trans-trans* isomers doubled after the infusion rate was increased from 5 to 10 µg/kg/min, indicating that their pharmacokinetics are dose-proportional.

Table 3
Stereoisomer Pharmacokinetic Parameters[1] of MIVACRON in ASA Physical Status I-II Adult Patients[2] [n=9] During Opioid/Nitrous Oxide/Oxygen Anesthesia

Parameter	*trans-trans* isomer	*cis-trans* isomer
Elimination Half-life ($t_{1/2}$, min)	2.3 (1.4-3.6)	2.1 (0.8-4.8)
Volume of Distribution (L/kg)	0.15 (0.06-0.24)	0.27 (0.08-0.56)
Plasma Clearance (mL/min/kg)	53 (32-105)	99 (52-230)

[1]Values shown are mean (range).
[2]Ages 31 to 48 years.

The *cis-cis* isomer (6% of the mixture) has approximately one-tenth the neuromuscular blocking potency of *trans-trans* and *cis-trans* isomers in cats. In the nine patients shown in Table 3, the volume of distribution of the

cis isomer averaged 0.31 L/kg (range: 0.18-0.46), the clearance averaged 4.2 mL/min/kg (range: 2.4-5.4), and the half-life averaged 55 minutes (range: 32-102). The neuromuscular blocking potency of the *cis-cis* isomer in humans has not been established; however, modeling of clinical pharmacokinetic-pharmacodynamic data suggests that the *cis-cis* isomer produces minimal (<5%) neuromuscular block during a two-hour infusion. In studies in which infusions of up to 2.5 hours were administered to ASA Physical Status I–II patients, the 25%-75% recovery times were independent of the duration of infusion, suggesting that the *cis-cis* isomer does not contribute significant neuromuscular block during use for up to 2.5 hours. Limited data are available from infusions of longer duration or from patients with compromised elimination capacities (hepatic or renal failure).

Metabolism and Excretion: *Enzymatic hydrolysis by plasma cholinesterase is the primary mechanism for inactivation of mivacurium and yields a quaternary alcohol and a quaternary monoester metabolite.* Renal and biliary excretion of unchanged mivacurium are minor elimination pathways; urine and bile are important elimination pathways for the two metabolites. Tests in which these two metabolites were administered to cats and dogs suggest that each metabolite is unlikely to produce clinically significant neuromuscular, autonomic, or cardiovascular effects following administration of MIVACRON.

Special Populations: The pharmacokinetics of mivacurium isomers has not been studied in the elderly or in patients with renal or hepatic disease using a stereospecific assay. The non-stereospecific, total mivacurium assay used in pharmacokinetic-pharmacodynamic studies in these populations provided preliminary evidence that reduced clearance of one or more isomers is responsible for the longer duration of action of MIVACRON seen in patients with end-stage kidney or liver disease. The data did not provide a pharmacokinetic explanation for the 15-20% longer duration of block seen in the elderly. Tables 4 and 5 summarize the pharmacodynamic results in these special populations as compared with young adults (ages 18 to 49 years). No data are available from patients with kidney or liver disease not requiring transplantation.

Table 4
Pharmacodynamic Parameters[1] of MIVACRON in ASA Physical Status I-II Young Adult Patients and Elderly Patients During Isoflurane/Nitrous Oxide/Oxygen Anesthesia

Parameter	Young Adult Patients (18-49 years)		Elderly Patients (68-77 years)
Initial Dose	0.10 mg/kg [n=9]	0.25 mg/kg [n=9]	0.10 mg/kg [n=8]
Maximum Block (%)	98 (83-100)	100 (100-100)	99 (95-100)
Time to Maximum Block (min)	3.2 (2.0-6.0)	1.7 (1.3-2.5)	4.8 (3.0-7.0)
Clinically Effective Duration of Block[2] (min)	17 (9-29)	27 (18-34)	20 (14-28)

[1]Values shown are mean (range).
[2]Time from injection to 25% recovery of the control twitch height.

Renal: The clinically effective duration of action of 0.15 mg/kg MIVACRON was about 1.5 times longer in patients with end-stage kidney disease than in healthy patients, presumably due to reduced clearance of one or more isomers.

Hepatic: The clinically effective duration of action of 0.15 mg/kg MIVACRON was three times longer in patients with end-stage liver disease than in healthy patients and is likely related to the markedly decreased plasma cholinesterase activity (30% of healthy patient values) which could decrease the clearance of one or more isomers (see **Reduced Plasma Cholinesterase Activity** subsection of PRECAUTIONS).

Table 5
Pharmacodynamic Parameters[1] of MIVACRON in ASA Physical Status I-II Patients and in Patients Undergoing Kidney or Liver Transplantation During Isoflurane/Nitrous Oxide/Oxygen Anesthesia

Parameter	Young Adult Patients	Kidney Transplant Patients	Liver Transplant Patients[3]
Initial Dose	0.15 mg/kg [n=8]	0.15 mg/kg [n=9]	0.15 mg/kg [n=8]
Maximum Block (%)	99.8 (98-100)	100 (100-100)	100 (100-100)
Time to Maximum Block (min)	1.9 (0.8-3.5)	2.6 (1.0-4.5)	2.1 (1.0-4.0)
Clinically Effective Duration of Block[2] (min)	19 (12-30)	30 (19-58)	57 (29-80)

[1]Values shown are mean (range).
[2]Time from injection to 25% recovery of the control twitch height.
[3]Liver transplant patients received isoflurane without nitrous oxide.

Individualization of Dosages: DOSES OF MIVACRON SHOULD BE INDIVIDUALIZED AND A PERIPHERAL NERVE STIMULATOR SHOULD BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING MIVACRON ADMINISTRATION IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DOSES, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

Based on the known actions of MIVACRON (a mixture of three stereoisomers) and other neuromuscular blocking agents, the following factors should be considered when administering MIVACRON:

Renal or Hepatic Impairment: A dose of 0.15 mg/kg MIVACRON is recommended for facilitation of tracheal intubation in patients with renal or hepatic impairment. However, the clinically effective duration of block produced by this dose is about 1.5 times longer in patients with end-stage kidney disease and about 3 times longer in patients with end-stage liver disease than in patients with normal renal and hepatic function. Infusion rates should be decreased by as much as 50% in these patients depending on the degree of renal or hepatic impairment (see **Renal and Hepatic Disease** subsection of PRECAUTIONS).

Reduced Plasma Cholinesterase Activity: The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. MIVACRON should be used with great caution, if at all, in patients known or suspected of being homozygous for the atypical plasma cholinesterase gene (see WARNINGS). Doses of 0.03 mg/kg produced complete neuromuscular block for 26 to 128 minutes in three such patients; thus initial doses greater than 0.03 mg/kg are not recommended in homozygous patients. Infusions of MIVACRON are not recommended in homozygous patients.

MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene and in genotypically normal patients with reduced plasma cholinesterase activity. After recommended intubating doses of MIVACRON, the clinically effective duration of block in heterozygous patients may be approximately 10 minutes longer than in patients with normal genotype and normal plasma cholinesterase activity. Lower MIVACRON infusion rates are recommended in these patients (see **Reduced Plasma Cholinesterase Activity** subsection of PRECAUTIONS).

Drugs or Conditions Causing Potentiation of or Resistance to Neuromuscular Block: As with other neuromuscular blocking agents, MIVACRON may have profound neuromuscular blocking effects in cachectic or debilitated patients, patients with neuromuscular diseases, and patients with carcinomatosis. In these or other patients in whom potentiation of neuromuscular block or difficulty with reversal may be anticipated, the recommended initial dose should be decreased. A test dose of not more than 0.015–0.020 mg/kg, which represents the lower end of the dose-response curve for MIVACRON, is recommended in such patients (see **General** subsection of PRECAUTIONS).

The neuromuscular blocking action of the stereoisomers in MIVACRON is potentiated by isoflurane or enflurane anesthesia. The recommended initial MIVACRON dose of 0.15 mg/kg may be used for intubation prior to the administration of these agents. If MIVACRON is first administered after establishment of stable-state isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC), the initial MIVACRON dose should be reduced by as much as 25%, and the infusion rate reduced by as much as 35% to 40%. A greater potentiation of the neuromuscular blocking action of the stereoisomers in MIVACRON may be expected with higher concentrations of enflurane or isoflurane. The use of halothane requires no adjustment of the initial dose of MIVACRON, but may prolong the duration of action and decrease the average infusion rate by as much as 20% (see **Drug Interactions** subsection of PRECAUTIONS).

When MIVACRON is administered to patients receiving certain antibiotics, magnesium salts, lithium, local anesthetics, procainamide and quinidine, longer durations of neuromuscular block may be expected and infusion requirements may be lower (see **Drug Interactions** subsection of PRECAUTIONS).

When MIVACRON is administered to patients chronically receiving phenytoin or carbamazepine, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher (see **Drug Interactions** subsection of PRECAUTIONS).

Severe acid-base and/or electrolyte abnormalities may potentiate or cause resistance to the neuromuscular blocking action of the stereoisomers in MIVACRON. No data are available in such patients and no dosing recommendations can be made (see **General** subsection of PRECAUTIONS).

Burns: While patients with burns are known to develop resistance to nondepolarizing neuromuscular blocking agents, they may also have reduced plasma cholinesterase activity. Consequently, in these patients, a test dose of not more than 0.015–0.020 mg/kg MIVACRON is recommended, followed by additional appropriate dosing guided by the use of a neuromuscular block monitor (see **General** subsection of PRECAUTIONS).

Cardiovascular Disease: In patients with clinically significant cardiovascular disease, the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds (see **Hemodynamics** subsection of CLINICAL PHARMACOLOGY and **General** subsection of PRECAUTIONS).

Obesity: Obese patients (patients weighing ≥30% more than their ideal body weight) dosed on the basis of actual body weight, thereby receiving a larger dose than if dosed on the basis of ideal body weight, had a greater probability of experiencing a decrease of ≥30% in MAP (see **Hemodynamics** subsection of CLINICAL PHARMACOLOGY and **General** subsection of PRECAUTIONS). Therefore, in obese patients, the initial dose should be determined using the patient's ideal body weight (IBW), according to the following formulae:

Men: IBW in kg = [106 + (6 x inches in height above 5 feet)]/2.2
Women: IBW in kg = [100 + (5 x inches in height above 5 feet)]/2.2

Allergy and Sensitivity: In patients with any history suggestive of a greater sensitivity to the release of histamine or related mediators (*e.g.*, asthma), the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds (see **General** subsection of PRECAUTIONS).

INDICATIONS AND USAGE: MIVACRON is a short-acting neuromuscular blocking agent indicated for inpatients and outpatients, as an adjunct to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: MIVACRON is contraindicated in patients known to have an allergic hypersensitivity to mivacurium chloride or other benzylisoquinolinium agents, as manifested by reactions such as urticaria or severe respiratory distress or hypotension. Use of MIVACRON from multi-dose vials is contraindicated in patients with a known allergy to benzyl alcohol.

WARNINGS: MIVACRON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS PERSONNEL AND FACILITIES FOR RESUSCITATION AND LIFE SUPPORT (TRACHEAL INTUBATION, ARTIFICIAL VENTILATION, OXYGEN THERAPY), AND AN ANTAGONIST OF MIVACRON ARE IMMEDIATELY AVAILABLE. IT IS RECOMMENDED THAT A PERIPHERAL NERVE STIMULATOR BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING THE ADMINISTRATION OF MIVACRON IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DRUG, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

MIVACRON HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

MIVACRON IS METABOLIZED BY PLASMA CHOLINESTERASE AND SHOULD BE USED WITH GREAT CAUTION, IF AT ALL, IN PATIENTS KNOWN TO BE OR SUSPECTED OF BEING HOMOZYGOUS FOR THE ATYPICAL PLASMA CHOLINESTERASE GENE.

MIVACRON Injection and MIVACRON Premixed Infusion are acidic (pH 3.5 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

Multiple dose vials of MIVACRON contain benzyl alcohol. In newborn infants, benzyl alcohol has been associated with an increased incidence of neurological and other complications which are sometimes fatal. Single use vials and MIVACRON Premixed Infusion do not contain benzyl alcohol.

PRECAUTIONS:

General: Although MIVACRON (a mixture of three stereoisomers) is not a potent histamine releaser, the possibility of substantial histamine release must be considered. Release of histamine is related to the dose and speed of injection.

Caution should be exercised in administering MIVACRON to patients with clinically significant cardiovascular disease and patients with any history suggesting a greater sensitivity to the release of histamine or related mediators (*e.g.*, asthma). In such patients, the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds; assurance of adequate hydration and careful monitoring of hemodynamic status are important (see **Hemodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

Obese patients may be more likely to experience clinically significant transient decreases in MAP than non-obese patients when the dose of MIVACRON is based on actual rather than ideal body weight. Therefore, in obese patients, the initial dose should be determined using the patient's ideal body weight (see **Hemodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

Recommended doses of MIVACRON have no clinically significant effects on heart rate; therefore, MIVACRON will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (*e.g.*, myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (*e.g.*, carcinomatosis), the use of a peripheral nerve stimulator and a dose of not more than 0.015–0.020 mg/kg MIVACRON is recommended to assess the level of neuromuscular block and to monitor dosage requirements (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

MIVACRON has not been studied in patients with burns. Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns, depending upon the time elapsed since the injury and the size of the burn. Patients with burns may have reduced plasma cholinesterase activity which may offset this resistance (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

No data are available to support the use of MIVACRON by intramuscular injection.

Renal and Hepatic Disease: The possibility of prolonged neuromuscular block must be considered when MIVACRON is used in patients with renal or hepatic disease (see **Pharmacokinetics** subsection of CLINICAL PHARMACOLOGY). Most patients with chronic hepatic disease such as hepatitis, liver abscess, and cirrhosis of the liver exhibit a marked reduction in plasma cholinesterase activity. Patients with acute or chronic renal disease may also show a reduction in plasma cholinesterase activity (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Reduced Plasma Cholinesterase Activity: The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity.

Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (*e.g.*, patients heterozygous or homozygous for the atypical plasma cholinesterase gene), pregnancy, liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Plasma cholinesterase activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (*e.g.*, organophosphate insecticides, echothiophate, and certain antineoplastic drugs).

MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. At doses of 0.10 to 0.20 mg/kg MIVACRON, the clinically effective duration of action was 8 to 11 minutes longer in patients heterozygous for the atypical gene than in genotypically normal patients.

As with succinylcholine, patients homozygous for the atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of MIVACRON. In three such adult patients, a small dose of 0.03 mg/kg (approximately the $ED_{10\text{-}20}$ in genotypically normal patients) produced complete neuromuscular block for 26 to 128 minutes. Once spontaneous recovery had begun, neuromuscular block in these patients was antagonized with conventional doses of neostigmine. One adult patient, who was homozygous for the atypical plasma cholinesterase gene, received a dose of 0.18 mg/kg MIVACRON and exhibited complete neuromuscular block for about 4 hours. Response to post-tetanic stimulation was present after 4 hours, all four responses to train-of-four stimulation were present after 6 hours, and the patient was extubated after 8 hours. Reversal was not attempted in this patient.

Malignant Hyperthermia (MH): In a study of MH-susceptible pigs, MIVACRON did not trigger MH. MIVACRON has not been studied in MH-susceptible patients. Because MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient undergoing general anesthesia.

Long-Term Use in the Intensive Care Unit (ICU): No data are available on the long-term use of MIVACRON in patients undergoing mechanical ventilation in the ICU.

Drug Interactions: Although MIVACRON (a mixture of three stereoisomers) has been administered safely following succinylcholine-facilitated tracheal intubation, the interaction between the stereoisomers in MIVACRON and succinylcholine has not been systematically studied. Prior administration of succinylcholine can potentiate the neuromuscular blocking effects of nondepolarizing agents. Evidence of spontaneous recovery from succinylcholine should be observed before the administration of MIVACRON.

The use of MIVACRON before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied.

There are no clinical data on the use of MIVACRON with other nondepolarizing neuromuscular blocking agents.

Isoflurane and enflurane (administered with nitrous oxide/oxygen to achieve 1.25 MAC) decrease the ED_{50} of MIVACRON by as much as 25% (see **Pharmacodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY). These agents may also prolong the clinically effective duration of action and decrease the average infusion requirement of MIVACRON by as much as 35% to 40%. A greater potentiation of the neuromuscular blocking effects of the stereoisomers in MIVACRON may be expected with higher concentrations of enflurane or isoflurane. Halothane has little or no effect on the ED_{50}, but may prolong the duration of action and decrease the average infusion requirement by as much as 20%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as the stereoisomers in MIVACRON include certain antibiotics (*e.g.*, aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine. Drugs that may enhance the neuromuscular blocking effects of mivacurium by a reduction in plasma cholinesterase activity include chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (see **Reduced Plasma Cholinesterase Activity** subsection of PRECAUTIONS).

Resistance to the neuromuscular blocking action of nondepolarizing neuromuscular blocking agents has been demonstrated in patients chronically administered phenytoin or carbamazepine. While the effects of chronic phenytoin or carbamazepine therapy on the action of the stereoisomers in MIVACRON are unknown, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. MIVACRON was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, the mouse lymphoma assay, the human lymphocyte assay, and the *in vivo* rat bone marrow cytogenetic assay.

Pregnancy: *Teratogenic Effects*: Pregnancy Category C. Teratology testing in nonventilated pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of MIVACRON revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of MIVACRON in pregnant women. Because animal studies are not always predictive of human response, and the doses used were subparalyzing, MIVACRON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The use of MIVACRON during labor, vaginal delivery, or cesarean section has not been studied in humans and it is not known whether MIVACRON administered to the mother has effects on the fetus. Doses of 0.08 and 0.20 mg/kg MIVACRON given to female beagles undergoing cesarean section resulted in negligible levels of the stereoisomers in MIVACRON in umbilical vessel blood of neonates and no deleterious effects on the puppies.

Nursing Mothers: It is not known whether any of the stereoisomers of mivacurium are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following administration of MIVACRON to a nursing woman.

Pediatric Use: MIVACRON has not been studied in children below the age of 2 years (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age).

Geriatric Use: MIVACRON was safely administered during clinical trials to 64 elderly (≥65 years) patients, including 31 patients with significant cardiovascular disease (see **General** subsection of PRECAUTIONS). The duration of neuromuscular block may be slightly longer in elderly patients than in young adult patients (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS:

Observed in Clinical Trials: MIVACRON (a mixture of three stereoisomers) was well tolerated during extensive clinical trials in inpatients and outpatients. Prolonged neuromuscular block, which is an important adverse experience associated with neuromuscular blocking agents as a class, was reported as an adverse experience in 3 of 2074 patients administered MIVACRON. The most commonly reported adverse experience following the administration of MIVACRON was transient, dose-dependent cutaneous flushing about the face, neck, and/or chest. Flushing was most frequently noted after the initial dose of MIVACRON and was reported in about 20% of adult patients who received the recommended dose of 0.15 mg/kg MIVACRON over 5 to 15 seconds. When present, flushing typically began within 1 to 2 minutes after the dose of MIVACRON and lasted for 3 to 5 minutes. Of 60 patients who experienced flushing after 0.15 mg/kg MIVACRON, one patient also experienced mild hypotension that was not treated, and one patient experienced moderate wheezing that was successfully treated.

Overall, hypotension was infrequently reported as an adverse experience in the clinical trials of MIVACRON. None of the 397 adults or 63 children who received recommended doses was treated for a decrease in blood pressure associated with the administration of MIVACRON. Above the recommended dosage range, 1% to 2% of healthy adults given ≥0.20 mg/kg over 5 to 15 seconds and 2% to 4% of cardiac surgery patients given ≥0.20 mg/kg over 60 seconds were treated for decreases in blood pressure associated with the administration of MIVACRON.

The following adverse experiences were reported in patients administered MIVACRON (all events judged by investigators during the clinical trials to have a possible causal relationship):

Incidence Greater Than 1% -

Cardiovascular:	Flushing (15%)

Incidence Less Than 1% -

Cardiovascular:	Hypotension, Tachycardia, Bradycardia, Cardiac Arrhythmia, Phlebitis
Respiratory:	Bronchospasm, Wheezing, Hypoxemia
Dermatological:	Rash, Urticaria, Erythema, Injection Site Reaction
Nonspecific:	Prolonged Drug Effect
Neurologic:	Dizziness
Musculoskeletal:	Muscle Spasms

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (*e.g.*, neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent. (see **Antagonism of Neuromuscular Block**). Overdosage may increase the risk of hemodynamic side effects, especially decreases in blood pressure. If needed, cardiovascular support may be provided by proper positioning of the patient, fluid administration, and/or vasopressor agent administration.

Antagonism of Neuromuscular Block:

ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED WHEN COMPLETE NEUROMUSCULAR BLOCK IS EVIDENT OR SUSPECTED. THE USE OF A PERIPHERAL NERVE STIMULATOR TO EVALUATE RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED.

Administration of 0.030 to 0.064 mg/kg neostigmine or 0.5 mg/kg edrophonium at approximately 10% recovery from neuromuscular block (range: 1 to 15) produced 95% recovery of the muscle twitch response and a T_4/T_1 ratio ≥75% in about 10 minutes. The times from 25% recovery of the muscle twitch response to T_4/T_1 ratio ≥75% following these doses of antagonists averaged about 7 to 9 minutes. In comparison, average times for spontaneous recovery from 25% to T_4/T_1 ≥75% were 12 to 13 minutes.

Patients administered antagonists should be evaluated for adequate clinical evidence of antagonism, *e.g.*, 5-second head lift and grip strength. Ventilation must be supported until no longer required.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see **Drug Interactions** subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block (see OVERDOSAGE).

DOSAGE AND ADMINISTRATION: MIVACRON SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

The dosage information provided below is intended as a guide only. Doses of MIVACRON should be individualized (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). Factors that may warrant dosage adjustment include but may not be limited to: the presence of significant kidney, liver, or cardiovascular disease, obesity (patients weighing ≥30% more than ideal body weight for height), asthma, reduction in plasma cholinesterase activity, and the presence of inhalational anesthetic agents. The use of a peripheral nerve stimulator will permit the most advantageous use of MIVACRON, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Adults:

Initial Doses:

A dose of 0.15 mg/kg MIVACRON administered over 5 to 15 seconds is recommended for facilitation of tracheal intubation for most patients. When administered as a component of a thiopental/opioid/nitrous oxide/oxygen induction-intubation technique, 0.15 mg/kg (2 x ED_{95}) MIVACRON produces generally good-to-excellent conditions for tracheal intubation in 2.5 minutes. Lower doses of MIVACRON may result in a longer time for development of satisfactory intubation conditions. Administration of MIVACRON doses above the recommended range (≥0.20 mg/kg) is associated with the development of transient decreases in blood pressure in some patients (see CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

In patients with clinically significant cardiovascular disease and in patients with any history suggesting a greater sensitivity to the release of histamine or other mediators (*e.g.*, asthma), the dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds (see PRECAUTIONS).

Clinically effective neuromuscular block may be expected to last for 15 to 20 minutes (range: 9 to 38) and spontaneous recovery may be expected to be 95% complete in 25 to 30 minutes (range: 16 to 41) following 0.15 mg/kg MIVACRON administered to patients receiving opioid/nitrous oxide/oxygen anesthesia. Maintenance dosing is generally required approximately 15 minutes following an initial dose of 0.15 mg/kg MIVACRON during opioid/nitrous oxide/oxygen anesthesia. Maintenance doses of 0.10 mg/kg each provide approximately 15 minutes of additional clinically effective block. For shorter or longer durations of action, smaller or larger maintenance doses may be administered.

The neuromuscular blocking action of MIVACRON is potentiated by isoflurane or enflurane anesthesia. The recommended initial MIVACRON dose of 0.15 mg/kg may be used to facilitate tracheal intubation prior to the administration of these agents; however, if MIVACRON is first administered after establishment of stable-state isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC), the initial MIVACRON dose may be reduced by as much as 25%. Greater reductions in the MIVACRON dose may be required with higher concentrations of enflurane or isoflurane. With halothane, which has only a minimal potentiating effect on MIVACRON, a smaller dosage reduction may be considered.

Continuous Infusion: Continuous infusion of MIVACRON may be used to maintain neuromuscular block. Upon early evidence of spontaneous recovery from an initial dose, an initial infusion rate of 9 to 10 µg/kg/min is recommended. If continuous infusion is initiated simultaneously with the administration of an initial dose, a lower initial infusion rate should be used (*e.g.*, 4 µg/kg/min). In either case, the initial infusion rate should be adjusted according to the response to peripheral nerve stimulation and to clinical criteria. On average, an infusion rate of 6 to 7 µg/kg/min (range: 1 to 15) may be expected to maintain neuromuscular block within the range of 89% to 99% for extended periods in adults receiving opioid/nitrous oxide/oxygen anesthesia. Reduction of the infusion rate by up to 35% to 40% should be considered when MIVACRON is administered during stable-state conditions of isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC). Greater reductions in the MIVACRON infusion rate may be required with greater concentrations of enflurane or isoflurane. With halothane, smaller reductions in infusion rate may be required.

Children:

Initial Doses: Dosage requirements for MIVACRON on a mg/kg basis are higher in children than adults. Onset and recovery of neuromuscular block occur more rapidly in children than adults (see CLINICAL PHARMACOLOGY). The recommended dose of MIVACRON for facilitating tracheal intubation in children 2 to 12 years of age is 0.20 mg/kg

administered over 5 to 15 seconds. When administered during stable opioid/nitrous oxide/oxygen anesthesia, 0.20 mg/kg of MIVACRON produces maximum neuromuscular block in an average of 1.9 minutes (range: 1.3 to 3.3) and clinically effective block for 10 minutes (range: 6 to 15). Maintenance doses are generally required more frequently in children than in adults. Administration of MIVACRON doses above the recommended range (>0.20 mg/kg) is associated with transient decreases in MAP in some children (see **Hemodynamics** subsection of CLINICAL PHARMACOLOGY). MIVACRON has not been studied in children below the age of 2 years.

Continuous Infusion: Children require higher MIVACRON infusion rates than adults. During opioid/nitrous oxide/oxygen anesthesia the infusion rate required to maintain 89% to 99% neuromuscular block averages 14 µg/kg/min (range: 5 to 31). The principles for infusion of MIVACRON in adults are also applicable to children (see above).

Infusion Rate Tables:

For adults and children the amount of infusion solution required per hour depends upon the clinical requirements of the patient, the concentration of MIVACRON in the infusion solution, and the patient's weight. The contribution of the infusion solution to the fluid requirements of the patient must be considered. Tables 6 and 7 provide guidelines for delivery in mL/hr (equivalent to microdrops/min when 60 microdrops = 1 mL) of MIVACRON Premixed Infusion (0.5 mg/mL) and of MIVACRON Injection (2 mg/mL).

Table 6
Infusion Rates for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia Using MIVACRON Premixed Infusion (0.5 mg/mL)

Patient Weight (kg)	Drug Delivery Rate (µg/kg/min)									
	4	5	6	7	8	10	14	16	18	20
	Infusion Delivery Rate (mL/hr)									
10	5	6	7	8	10	12	17	19	22	24
15	7	9	11	13	14	18	25	29	32	36
20	10	12	15	17	19	24	34	38	43	48
25	12	15	18	21	24	30	42	48	54	60
35	17	21	26	29	34	42	59	67	76	84
50	24	30	36	42	48	60	84	96	108	120
60	29	36	43	50	58	72	101	115	130	144
70	34	42	50	59	67	84	118	134	151	168
80	39	48	58	67	77	96	134	154	173	192
90	44	54	65	76	86	108	151	173	194	216
100	48	60	72	84	96	120	168	192	216	240

Table 7
Infusion Rates for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia Using MIVACRON Injection (2 mg/mL)

Patient Weight (kg)	Drug Delivery Rate (µg/kg/min)									
	4	5	6	7	8	10	14	16	18	20
	Infusion Delivery Rate (mL/hr)									
10	1.2	1.5	1.8	2.1	2.4	3.0	4.2	4.8	5.4	6.0
15	1.8	2.3	2.7	3.2	3.6	4.5	6.3	7.2	8.1	9.0
20	2.4	3.0	3.6	4.2	4.8	6.0	8.4	9.6	10.8	12.0
25	3.0	3.8	4.5	5.3	6.0	7.5	10.5	12.0	13.5	15.0
35	4.2	5.3	6.3	7.4	8.4	10.5	14.7	16.8	18.9	21.0
50	6.0	7.5	9.0	10.5	12.0	15.0	21.0	24.0	27.0	30.0
60	7.2	9.0	10.8	12.6	14.4	18.0	25.2	28.8	32.4	36.0
70	8.4	10.5	12.6	14.7	16.8	21.0	29.4	33.6	37.8	42.0
80	9.6	12.0	14.4	16.8	19.2	24.0	33.6	38.4	43.2	48.0
90	10.8	13.5	16.2	18.9	21.6	27.0	37.8	43.2	48.6	54.0
100	12.0	15.0	18.0	21.0	24.0	30.0	42.0	48.0	54.0	60.0

MIVACRON Premixed Infusion in Flexible Plastic Containers:

The flexible plastic container is fabricated from a specially formulated, nonplasticized, thermoplastic co-polyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of the chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

Instructions for Use:

1. Tear outer wrap at notch and remove solution container. Check for minute leaks by squeezing container firmly. If leaks are found, discard solution as sterility may be impaired.
2. Close flow control clamp of administration set.
3. Remove cover from outlet port at bottom of container.
4. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.
5. Suspend container from hanger.
6. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion.
7. Open flow control clamp to expel air from set. Close clamp.
8. Attach set to intravenous tubing.
9. Regulate rate of administration with flow control clamp.

Caution: Additives should not be introduced into this solution. Do not administer unless solution is clear and container is undamaged. MIVACRON Premixed Infusion is intended for single patient use only. The unused portion of the solution should be discarded.

Warning: Do not use flexible plastic container in series connections.

MIVACRON Injection Compatibility and Admixtures:

Y-site Administration: MIVACRON Injection may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

Studies have shown that MIVACRON Injection is compatible with:

- 5% Dextrose Injection USP
- 0.9% Sodium Chloride Injection USP
- 5% Dextrose and 0.9% Sodium Chloride Injection USP
- Lactated Ringer's Injection USP
- 5% Dextrose in Lactated Ringer's Injection
- Sufenta® (sufentanil citrate) Injection, diluted as directed
- Alfenta® (alfentanil hydrochloride) Injection, diluted as directed
- Sublimaze® (fentanyl citrate) Injection, diluted as directed
- Versed® (midazolam hydrochloride) Injection, diluted as directed
- Inapsine® (droperidol) Injection, diluted as directed

Compatibility studies with other parenteral products have not been conducted.

Dilution Stability: MIVACRON Injection diluted to 0.5 mg mivacurium per mL in 5% Dextrose Injection USP, 5% Dextrose and 0.9% Sodium Chloride Injection USP, 0.9% Sodium Chloride Injection USP, Lactated Ringer's Injection USP, or 5% Dextrose in Lactated Ringer's Injection is physically and chemically stable when stored in PVC (polyvinyl chloride) bags at 5°C to 25°C (41°F to 77°F) for up to 24 hours. Aseptic techniques should be used to prepare the diluted product. Admixtures of MIVACRON should be prepared for single patient use only and used within 24 hours of preparation. The unused portion of diluted MIVACRON should be discarded after each case.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions which are not clear and colorless should not be used.

HOW SUPPLIED: MIVACRON Injection, 2 mg mivacurium in each mL.

5 mL Single Use Vials. Tray of 10 (NDC 0081-0705-44).

10 mL Single Use Vials. Tray of 10 (NDC 0081-0705-95).

10 mL Multiple Dose Vials containing 0.9% w/v benzyl alcohol as a preservative (see WARNINGS concerning newborn infants). Tray of 10 (NDC 0081-0705-03).

20 mL Multiple Dose Vials containing 0.9% w/v benzyl alcohol as a preservative (see WARNINGS concerning newborn infants). Tray of 10 (NDC 0081-0705-01).

50 mL Multiple Dose Vials containing 0.9% w/v benzyl alcohol as a preservative (see WARNINGS concerning newborn infants). Box of 1 (NDC 0081-0705-02).

MIVACRON Premixed Infusion in 5% Dextrose Injection USP, 0.5 mg mivacurium in each mL.

50 mL (in a 100 mL unit) Flexible Plastic Containers. (NDC 0081-0709-01).

100 mL (in a 100 mL unit) Flexible Plastic Containers. (NDC 0081-0709-02).

STORAGE: Store MIVACRON Injection at room temperature of 15° to 25°C (59° to 77°F). Avoid exposure to direct ultraviolet light. DO NOT FREEZE.

Recommended storage for MIVACRON Premixed Infusion is room temperature (15° to 25°C/59° to 77°F). Avoid excessive heat. Avoid exposure to direct ultraviolet light. Protect from freezing.

U.S. Patent No. 4761418

BURROUGHS WELLCOME CO.
Research Triangle Park, NC 27709

MIVACRON Premixed Infusion
Manufactured for
BURROUGHS WELLCOME CO.
by Abbott Laboratories
North Chicago, IL 60064

Printed in U.S.A. January 1992 000028

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 4,761,418
Issue Date: August 2, 1988
For: NOVEL COMPOUNDS
Inventors: Roy A. Swaringen, Jr., Hassan A. El-Sayad, David A. Yeowell; John A. Savarese
Assignee: Burroughs Wellcome Co.; General Hospital Corporation

DECLARATION

To the Commissioner of Patents and Trademarks:

I, Lawrence A. Nielsen, residing at Chapel Hill, North Carolina, declare as follows:

1) That I am a patent agent authorized to practice before the United States Patent and Trademark Office and that my registration number is 29,682.

2) That I make this declaration as the agent of Burroughs Wellcome Co., a corporation of the State of North Carolina, having a place of business at 3030 Cornwallis Road, Research Triangle Park, North Carolina 27709 (hereinafter referred to as "Wellcome").

3) That United States Patent 4,761,418, issued August 2, 1988 (hereinafter referred to as the "Patent") is jointly assigned to Wellcome and General Hospital Corporation and that under the provisions of Article XII of the License Agreement between General Hospital Corporation and Wellcome, a redacted copy of which is attached herewith as EXHIBIT 3, Wellcome is authorized to apply for an extension of the term of the Patent on behalf of General Hospital Corporation.

4) That submitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156 of the Patent (hereinafter referred to as the "Application") on behalf of Wellcome requesting a 172 day extension of the term of the Patent.

6) That I believe that the Patent is subject to extension pursuant to 37 CFR 1.710.

7) That I believe that a 172 day extension of the term of the Patent is fully justified under 35 U.S.C. 156 and applicable regulations.

8) That I believe the Patent meets the conditions for the extension of the term of a patent as set forth in 37 CFR 1.720.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States patent 4,761,418, issued August 2, 1988, and any extensions thereof.

Lawrence A. Nielsen

Date: March 16, 1992

Lawrence A. Nielsen
Reg. No. 29,682
Agent for Burroughs Wellcome Co.

EXHIBIT 1

United States Patent [19]

Swaringen, Jr. et al.

[54] **NOVEL COMPOUNDS**

[75] Inventors: **Roy A. Swaringen, Jr., Durham, N.C.; Hassan A. El-Sayad, Nasr City, Egypt; David A. Yeowell, Chapel Hill, N.C.; John J. Savarese, Boxford, Mass.**

[73] Assignees: **Burroughs Wellcome Co., Research Triangle Park, N.C.; General Hospital Corporation, Boston, Mass.**

[21] Appl. No.: **756,025**

[22] Filed: **Jul. 17, 1985**

[30] **Foreign Application Priority Data**

Jul. 18, 1984 [GB] United Kingdom 8418303

[51] **Int. Cl.**[4] **A61K 31/47; C07C 401/14**
[52] **U.S. Cl.** **514/308; 546/140**
[58] **Field of Search** 546/140; 514/308

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,004,031	10/1961	Taylor et al.	546/140
4,179,507	12/1979	Stenlake et al.	546/140
4,192,877	3/1980	Savarese et al.	546/140
4,235,906	11/1980	Savarese et al.	546/140
4,491,665	1/1985	El-Sayad et al.	546/140

FOREIGN PATENT DOCUMENTS

0010119	4/1980	European Pat. Off. .
0054309	6/1982	European Pat. Off. .
0080682	6/1983	European Pat. Off. .
863717	3/1961	United Kingdom .
2002758A	2/1979	United Kingdom .
2061929B	5/1981	United Kingdom .
2061929A	5/1981	United Kingdom .

OTHER PUBLICATIONS

The Alkaloids, vol. X, 1968, pp. 402–403, 424–428.
Recherches Sur Les Poisons Curarisants De Synthese, Bovet et al., 1951.
Br. J. Pharmac., (1972), 44, 765–778.
J. Chem. Soc. Perkin Trans., 1, 1982, pp. 1068–2077.

[11] **Patent Number: 4,761,418**

[45] **Date of Patent: Aug. 2, 1988**

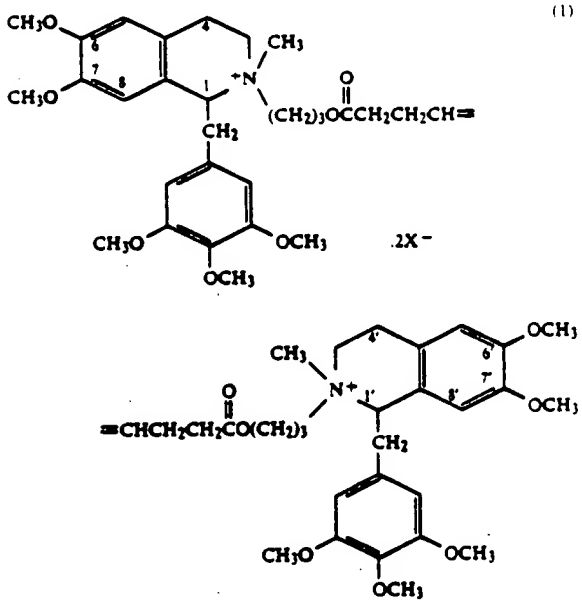
J. Chem. Soc. (C), 1966, S. M. Albonico et al.
Brit. J. Pharmacol., (1961), 17, 116–123.
Chem. Abstracts, vol. 71, 1969.
J. Chem. Soc., Gladych and Taylor, (1962).

Primary Examiner—Glennon H. Hollrah
Assistant Examiner—James H. Turnipseed
Attorney, Agent, or Firm—Donald Brown

[57] **ABSTRACT**

Neuromuscular blocking agents of formula (1) which are useful as skeletal muscle relaxants during surgery are disclosed.

(1)



and X is an anion, preferably pharmaceutically acceptable.

15 Claims, No Drawings

NOVEL COMPOUNDS

The present invention relates to novel compounds, method for the preparation of such compounds, pharmaceutical compositions containing them and their use in human and veterinary medicine as neuromuscular blocking agents of short duration.

In anesthesia, neuromuscular blocking agents are used to provide skeletal muscle relaxation during surgery and during intubation of the trachea. Neuromuscular blocking agents are used in practically every field of surgery.

In general there are two types of neuromuscular blocking agents in use, non-depolarizing and depolarizing.

The non-depolarizing agents include the long duration agents d-tubocurarine, pancuronium, gallamine, diallyltoxiferine, toxiferine, and the intermediate duration agents atracurium and vecuronium.

The depolarizing agents include succinylcholine and decamethonium. All the conventional non-depolarizing agents when used for producing skeletal muscle relaxation in surgery have a long duration of action, e.g. 60 to 180 minutes in humans. The conventional depolarizing agents, on the other hand, provide muscle relaxation with duration of action shorter than that of the non-depolarizing agents. For example, succinylcholine provides a short duration of action of about 5 to 15 minutes of muscle relaxation in humans.

The long-duration non-depolarizing agents have inherent side effects. For example, gallamine and pancuronium may cause tachycardia, and d-tubocurarine and diallyltoxiferine may cause hypotension. The intermediate duration and long duration non-depolarizing agents lack a rapid onset of neuromuscular paralysis.

While these non-depolarizing agents can be pharmacologically antagonized with anticholinesterase agents, this may necessitate the administration of a second drug which itself may have its own side effects, e.g., bradycardia, gut spasm and bronchorrhea. Thus, to overcome the aforementioned side effects of the anticholinesterase agents, a third drug, an anticholinergic agent, e.g., atropine, may also be given.

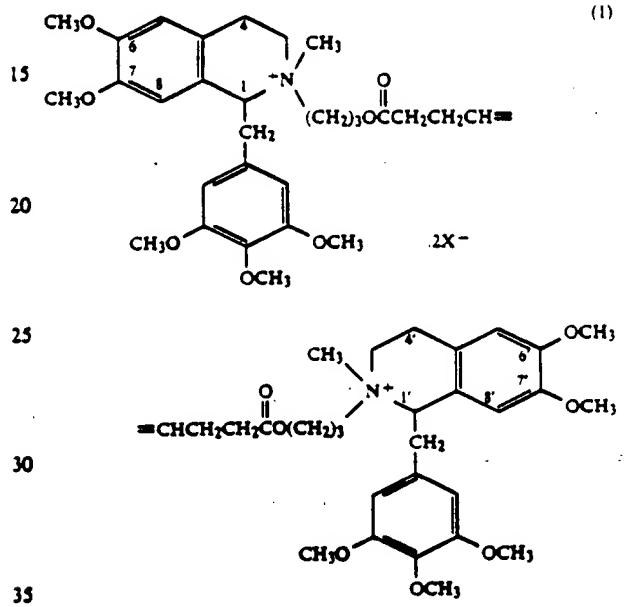
The only short-duration agent currently available for therapeutic use is the depolarizing agent, succinylcholine. The depolarizing agents to the best of the applicant's knowledge have no pharmacological antagonists and therefore cannot be reversed in patients who get into difficulty or if quicker recovery is desired. While in most cases there is no need to reverse the effects of the depolarizing agents, in certain patients the effects of succinylcholine are much prolonged because of abnormal metabolism of the agent by the patient.

The depolarizing agents due to their mode of action initially cause skeletal muscle contraction and stimulation of smooth muscles also cause the following side effects in certain instances: increased intraocular pressure, and intragastric tension, cardiac arrhythmias, potassium release and muscle pain.

These side effects caused by the depolarizing agents are not caused by the non-depolarizing agents. It is, therefore, clearly evident, and indeed has been recognized by clinicians for over 25 years, that a neuromuscular blocking agent which would combine the short duration of the depolarizing agents with the relatively few side effects and the pharmacologic reversibility of the non-depolarizing agents would be beneficial.

It has now been discovered that novel compounds of the formula (1) are potent neuromuscular blocking agents of relatively short duration, e.g., about ten minutes in monkeys. These compounds have a non-depolarising mechanism of action, are pharmacologically reversible and have a relatively rapid onset of action, a feature which is of great importance in emergency surgical procedures.

Accordingly, the present invention provides compounds of the formula (1):



(1)

wherein X^- is an anion.

The compounds of formula (1) contain a chiral center at the C(1) and C(1') carbon atoms of the isoquinolinium moieties and, therefore, may either the R or the S configuration exist at each center. The R configuration is that obtained using (−)-5'-methoxylaudanosine, also identified as (R)-(−)-5'-methoxylaudanosine, the preparation of which is described in the Example section. The compounds of formula (1) having the R configuration at both chiral centers are essentially free from significant side effects at the dosages that it is anticipated will be used clinically whereas the corresponding enantiomeric compounds, i.e., those having the S configuration at both centers, are likely to induce adverse cardiovascular effects, such as those associated with histamine release at clinically useful dosages. Accordingly, the compounds of formula (1), wherein the configuration at both the C(1) and the C(1') carbon atoms is the R configuration, constitute a preferred sub-class.

The compounds of formula (1) also contain an alkenic double bond and may, therefore, exist in either the E or the Z configuration, for example the E configuration. Moreover, the substituents about each of the quaternary nitrogen atoms may exist in either the R or the S configuration as well. As a result, for each of the geometric isomers (E or Z) of the preferred sub-class of compounds of formula (1) wherein the configuration at the C(1) and C(1') carbon atoms is the R configuration there are three diastereomers, the RR-RR, RS-RS and RR-RS. The RS-RR diastereomer is equivalent to the RR-RS Diastereomer thus, there are a total of six. The

present invention extends to these six diastereoisomers individually and as mixtures.

Within each set of diastereomers, the most potent are those having the RS-RS and the RS-RR configurations and are surprisingly more potent than the RR-RR diastereomers. However, the preferred embodiment within the scope of formula (1) in terms of potency and cost of manufacture is not any single diastereomer but the mixture of all three diastereomers. Within such a mixture, it is preferred that the RS-RS and RR-RS diastereomers together constitute the greater part, especially greater than 70% or even 80% or 90% (w/w). In fact, it is even more preferred that the mixture comprises from 1 to 15% (w/w) of the RR-RR diastereomer, from 38 to 50% (w/w) of the RR-RS diastereomer and from 40 to 56% (w/w) of the RS-RS diastereomer.

Since the pharmacological activity of the compounds of the invention resides in the di-cation, the nature of the anion X^- is relatively unimportant, although for therapeutic purposes it is, preferably, pharmaceutically acceptable to the recipient of the compounds. Examples of pharmaceutically acceptable anions include iodide, mesylate, tosylate, bromide, chloride, hydrogen sulphate, sulphate/2, phosphate/3, hydrogen phosphate/2, acetate, benzenesulphonate, hemisuccinate, succinate/2, maleate, naphthalenesulphonate and propionate. The pharmacologically acceptable salts together with the salts which are not thus acceptable have utility in the isolation and/or purification of the compounds of the invention, and the unacceptable salts are also useful in being convertible into the acceptable salts by techniques well known in the art.

The compounds of formula (1) are used as neuromuscular blocking agents in conjuction with surgery or for intubation of the trachea by conventional parenteral administration, e.g., intramuscular or intravenous administration in solution. Accordingly, the present invention also provides a method for producing muscle relaxation in a mammal, which comprises administering to the mammal an effective neuromuscular blocking amount of a compound of formula (1). In the alternative, there is provided a compound of formula (1) for use in human or veterinary medicine, especially for producing muscle relaxation in mammals. The compounds of the present invention are administered to subjects such as monkeys and humans and other mammals to achieve neuromuscular blockade. The dosage for each type of subject will vary because of the peculiarities of the species. However, a suitable intravenous amount or dosage of the compounds of formula (1) to obtain paralysis in mammals would be 0.01 to 0.50 mg/kg of body weight, and most preferably, 0.025 to 0.3 mg/kg of body weight, the above being based on the weight of the di-cation which is the active ingredient. The dosage for intramuscular administration is two to four times the intravenous dose. The compounds of this invention are reversible using conventional anticholinesterase agents such as neostigmine and edrophonium and appear to avoid the side effects associated with the conventional non-depolarizing agents.

The compounds of formula (1) are therefore useful for producing a short duration neuromuscular blockade in humans as well as in other mammals, and the present invention provides a method of producing such blockade in mammals by intravenously injecting a dose of 0.01 to 0.50 mg/kg to the mammal. It should be understood that the profile of neuromuscular blockade in a mammal such as monkey is similar to humans and the

compounds of formula (1) are considered as a short duration agent for the monkey.

While it is possible for compounds of formula (1) to be administered as the bulk active chemicals, it is preferred to present them in the form of a pharmaceutical formulation, in particular a pharmaceutical formulation for parenteral administration. Accordingly, the present invention provides a pharmaceutical formulation which comprises a compound of formula (1), as herein defined, and a pharmaceutically acceptable carrier.

In the preferred case where the pharmaceutical formulation is for parenteral administration, the formulation may be an aqueous or non-aqueous solution or emulsion in a pharmaceutically acceptable liquid or mixture of liquids, which may contain bacteriostatic agents, antioxidants, buffers, thickening agents, suspending agents or other pharmaceutically acceptable additives. Alternatively the compounds may be presented as lyophilized solids for reconstitution with water (for injection) or dextrose or saline solutions. Such formulations are normally presented in unit dosage forms such as ampoules or disposable injection devices, or in multidose forms such as a bottle from which the appropriate dose may be withdrawn; all such formulations should be sterile.

The suitable unit dose to obtain a neuromuscular block for adult humans (~150 lbs or 70 kg) is 0.5 to 30 mg and most preferably 3.5 to 15 mg.

The compounds of this invention if desired may be administered in conjunction with depolarizing agents such as listed above.

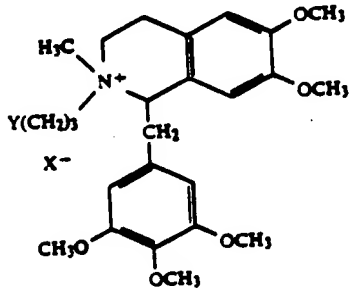
Thus a suitable pharmaceutical parenteral preparation for administration to humans will preferably contain 0.1 to 5 mg/ml of the compounds of formula (1) of this invention in solution or multiples thereof for multidose vials.

A simple and preferred formulation is a solution of the compound of formula (1) in water or dextrose solution which may be prepared by simply dissolving the compound in pyrogen-free water or water containing dextrose, with or without a preservative and sterilizing the solution, or by dissolving the sterile compound in pyrogen-free, sterile water or a sterile dextrose solution under aseptic conditions.

The compounds of formula (1) may also be administered as an infusion of a dextrose solution or a saline solution, e.g., Ringer's solution, in drip form.

The compounds may also be administered in other solvents (usually as a mixed solvent with water) such as alcohol, polyethylene glycol and dimethylsulphoxide. They may also be administered intramuscularly (as a drip if required) as a suspension or solution.

The compounds of formula (1) may be prepared by coupling a compound of formula (2):



(2)

wherein X^- is as defined hereinafter and Y can be hydroxy, chloro, bromo, iodo, or tosyloxy, with a compound of formula (3):

$$ZOCCH_2CH_2CH{=}CHCH_2CH_2COZ \quad (3)$$

wherein Z is hydroxy, chloro, bromo or C_{1-4} alkylcarbonyloxy, preferably chloro. At least one of Y and Z is always hydroxy.

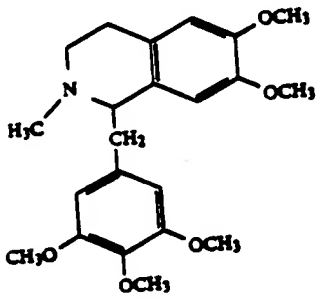
The coupling between the compounds of formulae (2) and (3) may be carried out conventionally, for example, by stirring a solution of the compounds, in which the compound of formula (2) is present in excess, in a solvent, such as 1,2-dichloroethane, at ambient or an elevated temperature.

The geometric configuration of the compound of formula (1) resulting from the coupling between the compounds of formulae (2) and (3) corresponds to the geometric configuration of the compound of formula (3). Thus, in order to obtain a compound of formula (1) with, say, the E-configuration, then the compound of formula (3) should also have the E-configuration.

The compound of formula (1), as obtained from the coupling between the compounds of formulae (2) and (3), is usually in the form of a mixture of optical isomers in which the RS-RS and the RR-RS optical isomers together account for the greater part of the mixture. If desired, one or more diastereomers can be separated from the mixture using conventional techniques for example chromatographic techniques.

The compound of formula (2) may be prepared by reacting a compound of formula (4):

(4)



with a compound of formula (5):

$$X{-}(CH_2)_3{-}OH \quad (5)$$

wherein X corresponds to the anion, X^-, defined hereinbefore; and optionally converting the anion X^- in the resulting compound of formula (2) into another anion.

The reaction between the compounds of formulae (4) and (5) is, preferably, carried out conventionally, for example, under reflux in a solvent, such as 2-butanone, in the presence of a base, such as sodium carbonate.

Preferably, X, in the compound of formula (5), is iodo, the compound being formed in situ from the corresponding compound of formula (5), wherein X is chloro, and sodium iodide.

In the preferred case where X, in the compound of formula (5), is iodo, the anion X^- in the compound of formula (2), resulting from the reaction between the compounds of formulae (4) and (5), is an iodide anion. In this case, it is preferred subsequently to convert the iodide anion in the resulting compound of formula (2)

into a pharmaceutically acceptable anion, such as the chloride anion, using conventional techniques.

The compounds of formulae (3), (4) and (5) are commercially available, or may be obtained by carrying out a published process for their preparation, or by carrying out a process analogous to a published process for the preparation of structurally analogous compounds.

The reached compounds of formula (2), on the other hand, are novel intermediates of use in the preparation of the compounds of formula (1), and, therefore, represent part of the present invention.

The present invention will now be described by reference to specific embodiments thereof.

GENERAL COMMENTS

All solvents and chemicals used were reagent grade and used without further purification. Analytical HPLC, unless otherwise noted, was performed on a Whatman Partisil 10 w (25 cm × 4.6 mm) column using a 20 μl sampling loop. The mobile phase used was methanol:ethyl acetate:trifluoroacetic acid:sulfuric acid: 61.1:38.5:0.3:0.1 at a flowrate of 2 mL/min. Detection was at 280 nm. While retention times (RT) vary with a number of factors, the order of elution is:

COMPOUNDS	RT
(E)—(1R,2R)—2-[3-[(7-Carboxy-4-heptenoyl)oxy]propyl]-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)-isoquinolinium chloride	150 sec
(E)—(1R,2S)—2-[3[(7-Carboxy-4-heptenoyl)oxy]propyl]-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)-isoquinolinium chloride	203 sec
cis-1,2,3,4-Tetrahydro-2-(3-hydroxypropyl)-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl) isoquinolinium chloride	250 sec
trans-1,2,3,4-Tetrahydro-2-(3-hydroxypropyl)-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl) isoquinolinium chloride	315 sec
2,2'[(E)—4-Octenedioylbis(oxytrimethylene)]bis[1R,2R—1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride	357 sec
(E)—(1R,1'R,2R,2'S)—2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethyoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride	519 sec
2,2'-[(E)—4-Octenedioylbis(oxytrimethylene)]bis[(1R,2S)—1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride	751 sec

All diesters were dried to constant weight at 0.1 mm Hg pressure and ambient temperature. Rotations are calculated on a volatiles-free basis.

EXAMPLE 1

2,2'[(E)-4-Octenedioylbis(oxytrimethylene)]bis[(trans)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride

a. Compound A: trans-1,2,3,4-Tetrahydro-2-(3-hydroxypropyl)-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl-)isoquinolinium chloride (trans quaternary chloride)

5'-Methoxylaudanosine (4.6 g), 3-chloropropanol (2.2 g), sodium iodide 3.5 g) and sodium carbonate (0.3 g) were refluxed in 2-butanone (45 mL) for 24 h. The white suspension was filtered hot and solvent was removed under vacuum. The resulting gum was triturated with diethyl ether to remove excess 3-iodopropanol. Residual solvent was removed under vacuum to give an amorphous solid which was assayed by HPLC as 6.3/1, trans/cis quaternary iodide salt. The material was dis-

solved in H_2O (45 mL), cooled to 0° C. and filtered to remove the precipitated cis isomer. Conversion to the chloride salt was accomplished by passing the trans enriched liquors through a column packed with Dowex ®1-X8 ion exchange resin (35 g). The eluant was concentrated under vacuum. Acetone trituration of the residual oil gave the chloride salt as a white solid. Slurrying the solids in dry N,N-dimethylformamide (20 mL) at 80° C. for 10 minutes removed the last traces of the cis isomer. The material was slurried in hot acetone to remove residual N,N-dimethylformamide and filtered to give 4.8 g (84%) of the quaternary chloride which was assayed by HPLC as 100% trans isomer: mp 212°-213° C.

Confirmation of the trans orientation was obtained by X-ray crystallographic analysis of the perchlorate salt of Compound A and reported in J. Chem. Soc. Perkin Trans I, 2067 (1982).

Calculated for $C_{25}H_{36}NO_6Cl$: C, 62.30; H, 7.53; N, 2.90; Cl, 7.36. Found: C, 62.35; H, 7.52; N, 2.91; Cl, 7.32.

b. Compound B:

cis-1,2,3,4-Tetrahydro-2-(3-hydroxypropyl)-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl-)isoquinolinium iodide (cis quaternary iodide)

5'-Methoxylaudanosine (47 g) and 3-iodopropanol (45 g) were refluxed in acetonitrile (500 mL) for 18 h. The solvent was removed under vacuum. The resulting gum was triturated with diethyl ether to remove excess 3-iodopropanol. Residual solvent was removed under vacuum to give an orange oil which was assayed by HPLC as 3/1, trans/cis quaternary iodide salt. The oil was dissolved in acetone (200 mL) and cooled at −5° C. for 18 h. The solid was filtered and dried for 2 h at 50° C. giving 37.1 g of the quaternary iodide mixture (3:1 trans:cis by HPLC). The solid was tritruated with water (200 mL) and filtered giving 10.5 g of purified cis quaternary iodide. Recrystallization from acetonitrile provided 7.7 g (11%) of white, crystalline solid: mp 142°-144° C.

Confirmation of the cis orientation was obtained by x-ray crystallographic analysis of Compound B and reported in J. Chem. Soc., Ibid.

Calculated for $C_{25}H_{36}NO_6IH_2O$: C, 50.80; H, 6.42; N, 2.36. Found: C, 50.74; H, 6.51; N, 2.34.

c. Compound C:

2,2'[(E)-4-Octenedioylbis(oxytrimethylene)]bis[(trans)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride

Trans-N-3-hydroxypropyl-5'-methoxylaudanosinium chloride (100% trans by HPLC, 5.9 g) was suspended in 80 ml 1,2-dichloroethane at −70° C. (E)-4-octene-1,8-dioic acid chloride (1.2 g) (K. Saido, K. Sei, H. Nozaki; *J. Org. Chem.*, 1962, 27, 2681) was added and the mixture was stirred at ambient temperature for 72 h. The reaction mixture was filtered and solvent was removed under vacuum to give an amorphous solid which was suspended in 1% aqueous sodium chloride solution. The suspension was adjusted to pH 8.0 with 1% sodium hydroxide and extracted with chloroform (3×200 mL). The combined chloroform extracts were evaporated to dryness. The residue was again suspended in 1% aqueous sodium chloride and the neutralization-extraction process was repeated as before. The combined chloroform portions were dried over anhydrous calcium chloride and filtered. The filtrate was evaporated to dryness. The residue was dissolved in 100 mL ethanol and evap-

orated to a foam which was further evaporated to constant weight under high vacuum (0.5 mm Hg). The white solid (2.8 g, 41%) was found to be 95% pure by HPLC.

Calculated for $C_{58}H_{80}N_2O_{14}Cl_2 5.1H_2O$: C, 58.44; H, 7.63; N, 2.21; Cl, 5.95. Found: C, 58.17; H, 7.34; N, 2.35; Cl, 6.07.

EXAMPLE 2

(+−)trans,
trans-2,2'-(Z)-4-Octenedioylbis(oxytrimethylene))-bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium dichloride
Compound D

Trans-N-3-hydroxypropyl-5'-methoxylaudanosinium chloride (Compound A, 100% trans by HPLC, 5.88 g) was suspended in 80 ml 1,2-dichloroethane at 70° C. and (Z)-4-Octene-1,8,-dioic acid chloride (1.2 g) was added. (A. Manzocchi, F. Astori, E. Sontaniello; *Synthesis*, 1983, 324. The diacid chloride was prepared as in Example 1). The mixture was stirred at ambient temperature for 16 h and filtered. The filtrate was concentrated to a foam and partitioned between water (65 mL) and nitromethane (15 mL). The aqueous portion was washed with diethyl ether and treated with sodium chloride (1.6 g). The brine solution was extracted with chloroform (40 mL). The chloroform extract was concentrated to a gum and subsequently dissolved in 2.5% aqueous sodium chloride solution (65 mL). The pH was adjusted to 9.0 with 0.1M sodium hydroxide and the aqueous solution extracted with chloroform (40 mL). The chloroform solution was washed with 5% aqueous sodium chloride (20 mL), dried over anhydrous calcium chloride, filtered and evaporated to a residue under reduced pressure. The solid was dissolved in ethanol (95%) and evaporated back down to a foam under reduced pressure. The foam was brought to constant weight under vacuum (0.5 mm Hg) giving 4.0 g (57%) of Compound D (92.2% by HPLC).

Calculated for $C_{58}H_{80}N_2O_{14}Cl_2 5.8H_2O$: C, 57.78; H, 7.69; N, 2.33; Cl, 5.89. Found: C, 57.83; H, 7.66; N, 2.33; Cl, 5.89.

EXAMPLE 3

(E)-(1R,1'R)-2,2'-[4-Octenedioylbis(oxytrimethylene)]-bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride
(Compound G)

a. Compound E: (R)-(−)-5'-Methoxylaudanosine

To (±)-5'-methoxylaudanosine (46.4 g) in methanol (240 mL) was added (−)-dibenzoyltartaric acid monohydrate (45.2 g). The mixture was heated to boiling, cooled at 5° C. for 16 h and the (S)-(−)-5'-methoxylaudanosinium dibenzoyltartrate salt (35.6 g, 80%) was filtered and discarded. The mother liquors were made basic with concentrated aqueous NaOH and evaporated under vacuum. The solid residue was partitioned between H_2O (200 mL) and diethyl ether (2×150 mL). The ether phase was dried and evaporated to an oil (24.9 g). To the oil in methanol (128 mL) was added (+)-dibenzoyltartaric acid monohydrate (26.6 g). The mixture was heated to boiling and cooled at 5° C. for 16 h. Crystals were collected and recrystallized from methanol until a constant specific rotation of $[\alpha]_D^{20} = +17.7°$ (1% EtOH) had been achieved. The yield of (R)-(+)-5'-methoxylaudanosinium dibenzoyl-

tartrate as white crystals was 29.4 g (66%). A portion of the salt (15.0 g) in methanol (200 mL) was made basic with concentrated aqueous NaOH. The mixture was evaporated under vacuum and the residue was partitioned between H_2O (200 mL) and diethyl ether (2×200 mL). The combined ether layers were dried and evaporated under vacuum to yield 7.2 g (92%) of (R)-(−)-5'-methoxylaudanosine as an oil.

b. Compound F

(R)-(−)-5'-Methoxylaudanosine (7.2 g), 3-chloropropanol (3.5 g), sodium iodide (5.6 g) and sodium carbonate (0.5 g) were refluxed in 2-butanone (125 mL) for 16 h. The white suspension was filtered hot and solvent removed from the filtrate under vacuum. The residual gum was trituated with hot ethyl acetate to remove excess 3-iodopropanol, dissolved in 200 mL methanol and passed through a column packed with Dowex ®1-X8 ion exchange resin (60 g chloride form). The eluant was stripped of solvent under vacuum to give the quaternary chloride salt (8.4 g) as an amophous solid. The material was assayed by HPLC as a 2.3/1 mixture of the trans/cis diastereomers.

c. Compound G

N-3-Hydroxypropyl-1-(R)-5'-methoxylaudanosinium chloride (2.3/1, trans/cis by HPLC, 2.5 g) was dissolved in 60 mL 1,2-dichloroethane at about 70° C. (E)-4-Octene-1,8-dioic acid chloride (0.5 g) (K. Sisido, K. Sei, and H. Nozaki, *J. Org. Chem.*, 1962, 27, 2681) was added and the mixture was stirred at ambient temperature for 19 h. Solvent was removed under vacuum to give an amorphous solid which was dissolved in chloroform (25 mL) and washed with 5% aqueous sodium chloride solution (3×35 mL) to remove unreacted quaternary salts. The chloroform layer was dried and evaporated under vacuum to give an amorphous solid. The acid ester impurities were substantially removed by washing with hot 2-butanone. Residual solvent was evaporated under vacuum and the resulting amorphous solid was dissolved in methanol, filtered and lyophilized to give 1.9 g of (E)-(1R,1'R)-2,2'-[4-octenedioylbis(oxytrimethylene)]-bis[1,2,4,3-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride, Compound G, which was assayed by HPLC as 44.6% RS-RS (trans-trans) diester, 42.4% RR-RS (cis-trans) diester, 7.5% RR-RR(cis-cis) diester, 4.0% RS (trans) acid ester and 1.5% RR (cis) acid ester. $[\alpha]_D^{20} = -62.7°$ (1.9% in H_2O).

Calculated for $C_{58}H_{80}N_2O_{14}.2Cl.4H_2O$: C, 59.44; H, 7.57; N, 2.39; Cl, 6.05. Found: C, 59.36; H, 7.60; N, 2.36; Cl, 5.99.

EXAMPLE 4

Chromatographic Separation of the Individual Components of Compound G

a.

A Waters HPLC/System 500A (Waters Associates, Milford, MA 01757) fitted with two silica gel cartridges in tandem was employed in this separation. The columns were pre-equilibrated in the mobile phase (ethanol:methanol:tetramethyl ammonium chloride: 600:400:1) and the diester mixture (Compound G, 5 g) in ethanol (25 ml) was loaded on the column. The system was eluted with 13.2 l of mobile phase which was col-

lected in 66 fractions (200 ml). The fractions were analyzed by analytical HPLC and combined as follows:

b. Compound H

(E)-(1R,1'R,2R,2'R)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride

Fractions 26–30 were combined and evaporated under reduced pressure. The resultant residue was triturated with chloroform (200 mL) and filtered. The fitrate was washed with 5% aqueous sodium chloride and concentrated to an oil under reduced pressure. The oil was dissolved in ethanol (50 mL) and evaporated to a foam (0.4 g): $[\alpha]_D^{20} = -33.6°$ (1.5% in H_2O); ^1H NMR ($CDCl_3$) from TMS: δ6.64 (s, H5, 2H), 6.27 (s, H2' and 6', 4H), 5.75 (s, H8, 2H).

Calculated for $C_{58}H_{80}N_2O_{14}Cl_2$, $3.7H_2O$, $0.9C_2H_5OH$, 0.3 $(CH_3)_4N^+Cl^-$: C, 59.02; H, 7.88; N, 2.62; Cl, 6.61. Found: C, 59.03; H, 7.83; N, 2.60; Cl, 6.57.

Compound H (10 mg) in 1% aqueous phoshoric acid (10 mL) was heated for 18 h at 60°–70° C. and analyzed by HPLC. The cis quaternary salt was observed to the exclusion of the trans quaternary salt. This was verified by co-injections with Compound A and with Compound B.

c. Compound I

(E)-(1R,1'R,2R,2'S)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethyoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride

Fractions 34–46 were combined and the product isolated in a manner analogous to Compound H. From this was obtained 2.0 g of a white foam: $[\alpha]_D^{20} = -54.0°$ (1.5% in H_2O); ^1H NMR ($CDCl_3$) from TMS: δ6.64 (s, H5, 2H), 6.42 and 6.25 (2s, H2' and 6', 4H), 5.75 (s, H8, 2H).

Calculated for $C_{58}H_{80}O_{14}Cl_2$, $1.5H_2O$, $1.3C_2H_5OH$: C, 61.28; H, 7.76; N, 2.36; Cl, 6.01. Found: C, 61.32; H, 7.71; N, 2.36; Cl, 5.97.

Compound I (10 mg) in 1% aqueous phosphoric acid (10 mL) was heated at 60°–70° C. for 18 h and analyzed by HPLC. Equal amounts of the cis and trans quaternary salts were observed. This was verified by co-injections with Compound A and with Compound B.

d. Compound J

(E)-(1R,1'R,2S,2'S)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride

Fractions 56–66 were combined and the product isolated in a manner analogous to Compound H. From this was isolated 0.9 g of an off-white foam: $[\alpha]_D^{20} = -76.7°$ [1.5% in H_2O]; ^1H NMR ($CDCl_3$) from TMS: δ6.64 (s, H5, 2H), 6.42 (s, H2' and 6', 4H), 5.76 (s, H8, 2H).

Calculated for $C_{58}H_{80}N_2O_{14}Cl_2$, $3.3H_2O$, $1.7C_2H_5OH$, $0.4(CH_3)_4NCl$: C, 59.02; H, 7.99; N, 2.63; Cl, 6.63. Found: C, 59.02; H, 7.99, N, 2.62; Cl, 6.64.

Compound J (10 mg) in 1% aqueous phosphoric acid (10 ml) was heated at 60°–70° C. for 18 hours and analyzed by HPLC. The trans quaternary salt was observed to the exclusion of the cis quaternary salt. This was verified by co-injection with Compound A and with Compound B.

EXAMPLE 5

Biological Activity

The tests employed herein are described by J. J. Savarese (*Anesthesia and Analgesia*, Vol. 52, No. 6, November-December, (1973). Cats were anesthetized with alpha-chloralose (80 mg/kg) and pentobarbital (10 mg/kg) i.p. Monkeys received thiopental (35–40 mg/kg) i.m. followed by halothane (0.5–10% inspired), nitrous oxide (60%) and oxygen (40%) in a nonrebreathing system. In all animals, the trachea was intubated and ventilation was controlled at 12–15 ml/kg, 18–24 breaths per minute. Animals not receiving inhalation anesthetics were ventilated with room air. The left femoral vein and artery were cannulated for drug administration and for recording of arterial pressure, respectively. Square-wave stimuli were applied at supramaximal voltage to the peroneal nerve at 0.15 Hz and the evoked twitches of the tibialis anterior muscle were recorded. Muscle and animal temperatures were maintained between 35° and 38° C. All recordings were made on a Grass Polygraph recorder. The results of these tests are shown in Table I and Table II below.

TABLE I

Direct Comparison of Compound G (diastereomeric Mixture) and Compound J (RS—RS Diastereomer of G) in Cats and Rhesus Monkey

	CAT[a]			RHESUS MONKEY[a]		
COMPOUND	dose[c] (mg/kg i.v.)	% block	duration[b] (min)	dose (mg/kg/i.v.)	% block	duration (min)
G (Example 3c)	0.04	56 ± 12	10 ± 2	0.02	27	6
	0.05	78 ± 10	13 ± 1	0.04	99	12
J (Example 4d)	0.04	79 ± 4	12 ± 2	0.02	83	11
	0.05	96 ± 3	12 ± 3	0.03	100	13

[a]n = 3 For the cat and n = 1 for the monkey.
[b]The time from intravenous injection to 95% recovery.
[c]Intravenous dose producing 95% neuromuscular paralysis of the tibialis anterior twitch extrapolated from dose-response curves. The ED_{95} neuro-muscular blocking dose is determined because it is related to the degree of muscular paralysis needed to safely facilitate a rapid and easy intubation when neuromuscular blocking agents are used therapeutically.

TABLE II

ED_{95} Values in Cats (Intravenous)

Compound	Number of Animals	ED_{95} mg/kg[b]
C	15	0.093 ± 0.005
D	10	0.086 ± 0.010
G	12	0.057 ± 0.005
H	5	>0.40
I	12	0.054 ± 0.004
J	15	0.054 ± 0.005

[b]The time from intravenous injection to 95% recovery.

Table I shows that in the cat and rhesus monkey Compound G and Compound J have the same neuromuscular blocking profiles except that in both species Compound J is at least 20–25 percent more potent than Compound G.

Table II lists the dose needed to produce 95% neuromuscular blockade (ED_{95}) in the animals in the test group for the compounds of formula (1) exemplified herein.

EXAMPLE 6

Toxicity

Three groups of four beagle dogs each were treated twice weekly for three weeks with vehicle, Compound G at five times the ED_{100} or Compound G at fifteen times the ED_{100}. Each treatment session consisted of an initial bolus injection followed by a continuous infusion for two hours. All of the dogs were anesthetized with

pentobarbital and artificially ventilated during the sessions. All of the dogs survived, and no deleterious effects were observed.

EXAMPLE 7

Formulation

Injection	Per 5 mL
Compound G	11.0 mg
HCl	q.s. pH 4.8
Water (for Injection)	q.s. 5 mL

The Active Ingredient, i.e. Compound G, is dissolved in 4.8 mL of water (for Injection), aqueous HCl is added to obtain the proper pH and additional water is added to reach a total volume of 5 mL. The resulting solution is filtered through a 2.2 micro meter membrane and sealed in vials or ampules under sterile conditions. Preferably, the formulation is stored under refrigeration (5°-10° C.) until use. Optionally, a preservative may be added to extend shelf life.

We claim:

1. 2,2'[(E)-4-Octenedioylbis(oxytrimethylene)]bis[(-trans)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] cation in association with a pharmaceutically acceptable anion.

2. 2,2'-[(E)-4-Octenedioylbis(oxytrimethylene)]bis[(-trans)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride.

3. (+−)trans,trans-2,2'-(Z)-4-Octenedioylbis(oxytrimethylene))bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium cation in association with a pharmaceutically acceptable anion.

4. (+−)trans,trans-2,2'-(Z)-4-Octenedioylbis(oxytrimethylene))bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium dichloride.

5. (E)-(1R,1'R)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] cation in association with a pharmaceutically acceptable anion.

6. (E)-(1R,1'R)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,4,3-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride.

7. (E)-(1R,1'R,2R,2'R)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]cation in association with a pharmaceutically acceptable anion.

8. (E)-(1R,1'R,2R,2'R)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride.

9. (E)-(1R,1'R,2R,2'S)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] cation in association with a pharmaceutically acceptable anion.

10. (E)-(1R,1'R,2R,2'S)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]chloride.

11. (E)-(1R,1'R,2S,2'S)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dication in association with a pharmaceutically acceptable anion.

12. (E)-(1R,1'R,2S,2'S)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride.

13. A method for producing muscle relaxation in a mammal which comprises parenterally administering to a mammal an effective muscle relaxant amount of the compound of claim 1, 3 or 5.

14. A sterile pharmaceutical composition comprising one or more of the compounds of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 in an effective muscle relaxant amount and a pharmaceutically acceptable solvent therefor.

15. A method for producing muscle relaxation in a mammal which comprises parenterally administering to a mammal an effective muscle relaxant amount of one or more of the compounds of claims 9, 10, 11 or 12.

* * * * *

EXHIBIT 2

(To Application for Extension of Patent Term of U.S. Patent 4,761,418

MIVACRON® Injection (Mivacurium Chloride)

Chronology of Major Activities During Regulatory Review Period[1]

Relating to IND 24,310

1.	06-07-84	Submitted Original IND.
2.	06-08-84	Letter from FDA acknowledging receipt of our Notice of Claimed Investigational Exemption for a New Drug (IND), and assigning IND Number 24,310.
3.	12-06-84	Letter from FDA commenting on the Chemistry & Pharmacology sections of our IND.
4.	04-11-85	Submitted response to manufacturing and controls questions raised in FDA letter of 12-6-84.
5.	06-19-85	Submitted Progress Report.
6.	11-18-85	Submitted response to FDA comments regarding the Preclinical, Pharmacology sections of the IND discussed in their correspondence of 12-6-84.
7.	02-24-86	Amended IND to provide for a new formulation; benzyl alcohol is being added as a preservative in order to package the product in a multiple-dose vial.
8.	03-07-86	Letter from FDA referencing our amendment of 11/18/85 recommending that this compound be tested for mutagenic potential.
9.	04-23-86	Telephone call to FDA requesting a meeting to discuss mutagenicity testing.
10.	05-05-86	Letter to FDA providing agenda for May 14, 1986 meeting to discuss mutagenicity testing requirements and clinical trials in women of childbearing potential.
11.	05-06-86	Telephone conversation with FDA to update them on the progress of the clinical studies.
12.	05-23-86	Submitted adverse reaction report on a patient who developed chest pain while being treated in clinical study 03.

[1]During the regulatory review period (June 7, 1984 through January 22, 1992), in addition to the activities specifically described in this EXHIBIT 3, Applicant had numerous additional communications with FDA in the form of submissions, meetings and telephone calls relating to IND 24,310 and NDA 20-098.

13.	05-27-86	Letter to FDA confirming agreements reached at May 14 meeting.
14.	05-29-86	Amended IND to provide for the use of an alternate stopper in the packaging of Mivacurium Dichloride Injection used in clinical trials.
15.	06-18-86	Submitted progress report.
16.	06-19-86	Submitted proposed agenda, clinical update and development plans for meeting to be held July 9, 1986.
17.	08-05-86	Amended IND to provide for modification to the synthesis of the drug substance.
18.	09-05-86	Letter from FDA informing us that women of childbearing potential can be enrolled in clinical trials.
19.	12-08-86	Letter to FDA presenting an outline of proposed safety and efficacy studies for the clinical development of Mivacurium Chloride.
20.	03-27-87	Informed FDA of our intention to include in our final reports for study 14 and study 13, validation information on the sensitivity, linearity, reproducibility and specificity of the HPLC assay.
21.	06-10-87	Telephone call from FDA suggesting that the scheduling of an End-of-Phase II Conference be delayed until a new medical reviewer is assigned.
22.	07-08-87	Submitted progress report.
23.	08-03-87	Letter to FDA requesting an End-of-Phase II conference.
24.	10-07-87	Telephone call from FDA requesting modifications to the inclusion criteria.
25.	12-04-87	Submitted preclinical reports.
26.	04-05-88	Letter from FDA.
27.	07-26-88	Submitted preclinical reports.
28.	09-07-88	Submitted Annual Report.
29.	12-02-88	Submitted preclinical report.
30.	05-10-89	Letter from FDA.
31.	11-13-89	Submitted Annual Report.
32.	02-28-90	Panafaxed a letter to FDA to accept their invitation to participate in a session on guidelines for the development of neuromuscular blocking agents and to suggest that an FDA Advisory Committee review of mivacurium should be scheduled after their review of our NDA.
33.	09-12-90	Submitted Annual Report for the period that covers June 8, 1989 through June 7, 1990.

34. 11-18-91 Submitted an IND Annual Report which covers the Period of June 8, 1990 to June 7, 1991.

RH/rc*/3

EXHIBIT 2 (con't)

(To Application for Extension of Patent Term of U.S. Patent 4,761,418

MIVACRON® Injection (Mivacurium Chloride)

Chronology of Major Activities During Regulatory Review Period

Relating to NDA 20-098

1.	08-30-90	Submitted original New Drug Application.
2.	09-13-90	Letter from FDA acknowledging receipt of our original NDA submitted August 30, 1990; stating the application will be considered filed on October 22, 1990, and February 26, 1991 is set for the review due date.
3.	10-18-90	In response to October 12, 1990 FDA request, provided a listing of clinical trials demonstrating substantial evidence of mivacurium effectiveness as a neuromuscular blocking agent and provided a listing of the 13 pivotal studies.
4.	10-18-90	Telephone call from FDA requesting specific study information in connection with GCP inspection to be conducted.
5.	01-04-91	Submitted a four month safety update to our original NDA.
6.	05-13-91	Received FDA letter by panafax requesting additional information to aid in the pharmacokinetic review of the original NDA.
7.	06-26-91	As requested, provided 30 copies of Item 2 of our NDA, (with labeling annotated to Item 2) to FDA for distribution to Advisory Committee members for their review.
8.	07-16-91	Letter to FDA with suggestions pertaining to the Advisory Committee review of the Mivacron summary materials delivered on June 25, 1991.
9.	08-28-91	Submitted a revised package insert updated to be consistent with wording for NUROMAX® Injection (doxacurium chloride).
10.	09-09-91	Letter to FDA in responds to their July 15, 1991 letter concerning the chemistry, manufacturing, and controls section of the NDA.
11.	09-24-91	Provided FDA with revised labeling to be used for the initial marketing of MIVACRON®.
12.	09-30-91	Telephone conversation with FDA review chemist regarding the sterilization cycles for this product.
13.	10-03-91	Submitted to FDA, the latest results with Mivacurium isomers.
14.	10-09-91	As requested by FDA during conversations on September 24 and 30, 1991, submitted data supporting the microbiological review of the NDA and data supporting a revision in the pH specification range.

RH/rc*/4

15.	11-05-91	As specified in our October 9, 1991 amendment to the NDA, submitted validation data supporting the efficacy of the terminal sterilization cycle.
16.	11-18-91	Provided FDA with revised proposed package insert.
17.	11-19-91	Received by panafax from FDA comments and recommendations from the chemistry review of the NDA.
18.	11-19-91	Provided FDA with copies of the patents for atracurium besylate, doxacurium chloride and mivacurium chloride as requested in November 6, 1991 telephone conversation.
19.	11-26-91	Provided FDA Advisory Committee members with package of information containing: 1) the most current annotated package insert; and 2) Item 2 (Application Summary) in which FDA review summaries were inserted.
20.	11-20-91	Received by panafax from FDA questions relating to the clinical review of the NDA.
21.	11-27-91	Letter to FDA responding to chemistry and manufacturing comments contained in their November 18, 1991 draft letter; confirmed B.W.'s willingness to meet on December 16, 1991 to discuss any outstanding chemistry issues.
22.	11-27-91	Conference call with FDA to discuss list of 26 questions/comments from FDA review of the pharmacokinetics section of the original NDA.
23.	12-06-91	Submitted a Safety Update Report covering the period October 16, 1990 - November 8, 1991.
24.	12-06-91	Letter to FDA providing statistical analyses of the updated stability data as committed to in November 27, 1991 response.
25.	12-16-91	Letter to FDA, providing them updated information from Abbott Laboratories regarding the fill volume of the 50 mL MIVACRON® PREMIX container as committed to in our November 27, 1991 letter to FDA.
26.	12-16-91	As committed in our October 9, 1991 amendment, provided FDA with data supporting a change to the range of in-process pH adjustment for MIVACRON® Infusion Premixed.
27.	12-16-91 and 12-17-91	NDA Day.
28.	12-19-91	As agreed in December 16, 1991 meeting between FDA and B.W. Co. members, submitted a listing of commitments pertaining to outstanding chemistry, manufacturing and controls issues as well as data responding to comments from FDA's review of the chemistry section.
29.	12-31-91	Submitted a revised package insert containing all labeling changes made since NDA Day.

30. 01-22-92 Letter from FDA approving the NDA and requesting revised labeling.

RH/rc*/6

EXHIBIT 3

LICENSE AGREEMENT

CONFIDENTIAL

This Agreement executed in duplicate as of the 1st day of July, 1985, by and between The General Hospital Corporation, a not-for-profit corporation of the Commonwealth of Massachusetts d.b.a. Massachusetts General Hospital and located at 55 Fruit Street, Boston, Massachusetts 02114 (hereinafter called "MGH") and Burroughs Wellcome Co., a corporation organized and existing under the laws of the State of North Carolina and having its principal place of business at 3030 Cornwallis Road, Research Triangle Park, North Carolina 27709 (hereinafter called "Wellcome").

WITNESSETH:

WHEREAS Wellcome has for a number of years provided to MGH funding for work by Dr. John Savarese with respect to muscle relaxant compounds;

WHEREAS John Savarese pursuant to said funding has consulted with Wellcome with respect to ongoing work of Wellcome with respect to such muscle relaxant compounds;

WHEREAS in meetings with Wellcome various muscle relaxant compounds to be made were discussed among John Savarese and various Wellcome employees;

WHEREAS, as a result of such discussion, Dr. Hassan El Sayad, Dr. David Yeowell and Dr. Roy Swaringen, all of whom are employees of Wellcome, and Dr. John Saverese have made inventions pertaining to new muscle relaxant compounds which are set

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forth in British Patent Application No. 8418303, filed July 18, 1984;

WHEREAS such new muscle relaxant compounds were synthesized and isolated at Wellcome by Wellcome employees and further testing, trials, and development will necessitate Wellcome's making further substantial investments of money in order to pursue development of one or more of such muscle relaxant compounds; and

WHEREAS MGH wishes to provide Wellcome with the incentive to make such further investment that will be needed to develop one or more of such muscle relaxant compounds;

NOW THEREFORE, in consideration of the mutual covenants hereinafter set forth and other good and valuable consideration, receipt of which is hereby acknowledged, the parties agree as follows:

ARTICLE I. DEFINITIONS

For purposes of this Agreement:

A. "MR Compounds" means any compound which is claimed in a Licensed Patent or made by a process claimed in a Licensed Patent.

B. "Product" means an MR Compound or any product containing one or more MR Compounds.

C. "Combination Product" means any Product containing one or more biologically active ingredients in addition to any of the MR Compounds.

D. "Licensed Patents" means British Patent Application No. 8418303 filed July 18, 1984, each other patent application

whether now or hereafter filed anywhere in the world corresponding to such British Patent Application, and each patent arising from such patent applications, and any addition, division, continuation, continuation-in-part, substitution, extension, renewal, or reissue thereof or therefor of such applications or patents.

E. "Technical Information" means information which is disclosed or required to be disclosed by MGH to Wellcome pursuant to the terms of this Agreement relating to MR Compounds or Products, including but not limited to manufacture, formulation, system of delivery, method of administration, analysis, stability, pharmacology, toxicology, pathology, clinical effects and methods of and indications for use of MR Compounds or Products.

F. "Net Sales" with respect to any Product other than a Combination Product shall mean the gross sales of such Product billed to independent customers by Wellcome and its sublicensees, less actual credited allowances to such independent customers for spoiled, damaged, out-dated and returned product and for retroactive price reductions and less the amounts of trade and cash discounts allowed by Wellcome, transportation and handling charges payable and all sales taxes, excise taxes or duties actually paid by Wellcome or its sublicensees, and less all other invoiced allowances and adjustments actually credited to customers, whether during the specific royalty period or not.

G. "Net Sales" with respect to any Combination Product shall mean the gross sales of such Combination Product billed to independent customers by Wellcome or its sublicensees, less all the allowances, adjustments, reductions, discounts, taxes, duties and other charges referred to in Paragraph F, above, multiplied by a

fraction the numerator of which shall be the manufacturing or acquisition cost of the MR Compound or Compounds included in such Combination Product and the denominator of which shall be the manufacturing or acquisition cost of all the active therapeutic ingredients in such Combination Product, including the MR Compound or Compounds, such cost to be determined by Wellcome or its sublicensees, as appropriate, in accordance with such party's customary accounting procedures.

H. "Valid Claim" means a claim of an issued and unexpired patent included within the Licensed Patents which has not been held unenforceable, unpatentable or invalid by a decision of a court or other governmental agency of competent jurisdiction, unappealable or unappealed within the time allowed for appeal, and which has not been admitted to be invalid or unenforceable through reissue or disclaimer or otherwise.

I. "Affiliate" means any corporation which controls, is controlled by, or is under common control with, a party to this Agreement. A corporation shall be regarded as in control of another corporation if it owns or directly or indirectly controls at least 40% of the voting stock of the other corporation or in the absence of the ownership of at least 40% of the voting stock of the corporation, if it possesses, directly or indirectly, the power to direct or cause the direction of the management and policies of the corporation.

J. "Territory" means the entire world.

K. "Third Party" means any party other than MGH, Wellcome and sublicensees of Wellcome.

ARTICLE II. WARRANTY

MGH warrants that it is the assignee and exclusive owner of all right, title and interest of Dr. John Savarese as a co-inventor of MR Compounds; and that it is free to enter into this Agreement and to carry out all of the provisions hereof including its agreement to grant to Wellcome an exclusive license with respect to MR Compounds and Products in the Territory.

ARTICLE III. GRANT

A. MGH hereby grants to Wellcome and Wellcome hereby accepts an exclusive license under the Licensed Patents, with right to sublicense, to make, have made, use, and sell, and to induce others to use and sell, MR Compounds and Products in the Territory.

B. MGH agrees that during the term of this Agreement it will not assert against Wellcome or its sublicensees any patent which (1) names John Savarese, M.D., as inventor or co-inventor, (2) is not included in the Licensed Patents and (3) is or might be infringed by Wellcome or its sublicensees by reason of its or their manufacture, use or sale of Products.

C. MGH agrees that Wellcome has the right to use Technical Information for any purpose so long as such use does not infringe any MGH patent, excluding however, Licensed Patents and patents which MGH has agreed under Paragraph B above not to assert against Wellcome.

ARTICLE IV. ROYALTIES

A. In consideration of the license granted herein, Wellcome shall pay or cause to be paid to MGH in respect of its and its sublicensees' Net Sales of Products in each country of the Territory a royalty equal to of such Net Sales. Such royalties shall be payable with respect to sales of a Product in a given country for a period of from the date of first commercial sale of a Product in such country. Thereafter, such royalties shall be paid only so long as the manufacture, use or sale of the Product in such country would, but for the license granted herein, infringe a Valid Claim of a Licensed Patent.

B. No royalties shall be payable on Net Sales in the United States until the United States Government has given Wellcome, or a sublicensee of Wellcome, approval to market a Product. Likewise, no royalties shall be payable on Net Sales in any foreign countries on a Product until the respective governmental approval for marketing is given in that respective foreign country. No royalties shall be payable on any MR Compound or Product made, sold, or used for test or developmental purposes. No royalties shall be payable on sales among Wellcome and its sublicensees, but royalties shall be payable on subsequent sale by Wellcome or its sublicensees to a Third Party.

C. No multiple royalties shall be payable because the manufacture, use or sale of a Product is covered by more than one patent.

ARTICLE V. ROYALTY PAYMENT AND ACCOUNTING

A. During the term of this Agreement, Wellcome shall furnish or cause to be furnished to MGH a written report or reports covering Wellcome's fiscal half years (ending on or about the last day of February and August) showing (1) the gross sales and the Net Sales of all Products sold by Wellcome and its sublicensees in the Territory during the reporting period; (2) the royalties, payable in U.S. dollars, which shall have accrued hereunder in respect of such sales; (3) withholding taxes, if any, required by law to be deducted in respect of such sales; and (4) the exchange rates used in determining the amount of U.S. dollars. With respect to sales of Products invoiced in U.S. dollars, the gross sales, Net Sales, and royalty payable shall be expressed in U.S. dollars. With respect to sales of Products invoiced in a currency other than U.S. dollars, the gross sales, Net Sales, and royalty payable shall be expressed in the domestic currency of the party making the sale together with the U.S. dollar equivalent of the royalty payable, calculated using the appropriate selling rate for such currency quoted in the Continental terms method of quoting exchange rates (local currency per U.S. $1) in New York City, New York, on the last day of the reporting period. If any sublicensee makes any sales invoiced in a currency other than its domestic currency the gross sales and Net Sales shall be converted to its domestic currency in accordance with the sublicensee's normal accounting practice which shall be in accordance with generally accepted accounting principles. Wellcome or its sublicensee making any royalty payment shall furnish to MGH appropriate evidence of payment of any

tax or other amount deducted from any royalty payment. Reports shall be due on the sixtieth (60th) day following the close of each respective semiannual period. In case no royalty is due for any royalty period hereunder, Wellcome shall so report. Wellcome shall keep accurate records in sufficient detail to enable the royalties payable hereunder to be determined.

B. Upon the written request of MGH, at MGH's expense and not more than once in each fiscal year (Wellcome's fiscal year ends on or about the last day of August), Wellcome shall permit an independent public accountant selected by MGH and acceptable to Wellcome, which acceptance shall not be unreasonably refused, to have access during normal business hours to such of the records of Wellcome as may be reasonably necessary to verify the accuracy of the royalty reports hereunder in respect of any fiscal year ending not more than two (2) fiscal years prior to the date of such request. Wellcome shall include in each sublicense granted pursuant to this Agreement a provision requiring the sublicensee to keep and maintain records of sales made pursuant to such sublicense and to grant access to such records by MGH's independent accountant. Upon the expiration of twenty-four (24) months following the end of any fiscal year, the calculation of royalties payable with respect to such year shall be binding and conclusive upon MGH; and Wellcome and its sublicensees shall be released from any liability or accountability with respect to royalties for such year.

C. MGH agrees that all information subject to review under this Article V or under any sublicense agreement is confidential and that MGH shall and shall cause its accountant to retain all such information in confidence.

ARTICLE VI. ROYALTY PAYMENTS

A. Royalties shown to have accrued by each royalty report provided for under Article V of this Agreement shall be due and payable on the date such royalty report is due. Payment of royalties in whole or in part may be made in advance of such due date.

B. Except as hereinafter provided in this Article VI(B), all royalties due to MGH hereunder shall be paid in U.S. currency. If at any time legal restrictions prevent the prompt remittance of part or all royalties by Wellcome or any sublicensee with respect to any country of the Territory where Product is sold, Wellcome or such sublicensee shall have the right and option to make such payments by depositing the amount thereof in local currency to MGH's account in a bank or other depository in such country.

C. In the event that the claims included within Licensed Patents under which Wellcome is selling or actively developing a Product shall be held invalid or not infringed by a court of competent jurisdiction, whether or not there is a conflicting decision by another court of competent jurisdiction, Wellcome shall not be obligated to make further royalty payments on sales covered by such claims until such judgment shall be finally reversed by an unappealed or unappealable decree of a court of competent jurisdiction of higher dignity, in which event royalty payments shall be resumed and the payments not theretofore made shall become due and payable.

ARTICLE VII. DEVELOPMENT

During each year of this Agreement ending on or before the filing by Wellcome of a New Drug Application for approval to market commercially a Product in the United States, Wellcome agrees to expend toward the development of a Product the sum of at least in manpower, supplies, or services, or in funding any other party, including MGH, or in any combination of the above. Wellcome may include in such sum of any expenditures made by any party having a sublicense from Wellcome or by any Affiliate of Wellcome.

ARTICLE VIII. TERM; TERMINATION

A. Unless terminated sooner pursuant to the provisions of Paragraphs B or C hereof, this Agreement shall expire upon expiration of all issued patents included in the Licensed Patents. Upon expiration, the rights and obligations of the parties hereunder shall cease except (1) for the right of Wellcome to use Technical Information furnished to it hereunder, and (2) the obligation of MGH under Article IV to keep certain information confidential, both of which shall survive such expiration.

B. MGH may not terminate this Agreement prior to its expiration as provided above, except that upon written notice to Wellcome

(1) MGH may terminate this Agreement in the event that

(a) Wellcome, after receipt of written notice to pay royalties due and owing MGH, fails to pay such royalties within sixty (60) days of such notice; or

(b) Wellcome is found to be insolvent or bankrupt by an unappealed or unappealable decree of a court of competent jurisdiction or makes or executes an assignment for the benefit of creditors; and

(2) MGH may terminate this Agreement with respect to a given country of the Territory in the event that

(a) Wellcome determines, in its sole discretion, neither to market nor to cause to be marketed through a sublicensee at least one Product in such country; or

(b) only one Product is being marketed in such country by Wellcome or its sublicensees; the marketing of such Product in such country ceases; and neither Wellcome nor its sublicensees intend to resume marketing such Product or to commence marketing another Product in such country.

C. Wellcome may terminate this Agreement at any time upon written notice to MGH. Such termination may be made with respect to one or more countries without affecting this Agreement or the licenses granted hereunder in any other country.

D. Termination of this Agreement by either party shall release Wellcome from all of its obligations hereunder except for the obligation to pay royalties accrued and unpaid up to the date of such termination.

ARTICLE IX. INFORMATION

During the term of this Agreement, MGH agrees promptly to provide to Wellcome or Wellcome's designee, at Wellcome's expense, all Technical Information in MGH's possession to aid Wellcome and its sublicensees in gaining approval of the U.S. and/or any foreign government to market Products.

ARTICLE X. INFRINGEMENT

In the event that any person shall infringe a patent included in the Licensed Patents, Wellcome shall have the sole right to file a suit, which shall be at its expense, to terminate such infringement. MGH agrees to permit itself to be joined or named in any such suit and will provide reasonable assistance at its own expense in the prosecution of any such suit. Any damages or costs recovered in connection with such suits shall be the property of Wellcome. Nothing herein obligates Wellcome to enter into any litigation of any nature whatsoever with regard to Licensed Patents.

ARTICLE XI. PATENT FILINGS, PROSECUTION, MAINTENANCE, AND EXPENSE

A. Wellcome or one of its Affiliates may file and control the prosecution of all United States and foreign patent applications based upon or corresponding to British Patent Application No. 8418303, filed July 18, 1984, and any divisions, continuations, continuations-in-part, or reissues thereof. Such patent applications may be filed in name of MGH as a joint owner, or in the names of the inventors with MGH being named as a joint owner. Wellcome will notify MGH of the countries in which it or one of its Affiliates intends to file such patent applications. If Wellcome or one of its Affiliates decides not to file, or having filed, to abandon or allow to lapse any such patent applications or to abandon or allow to lapse any patents issued pursuant to any such patent applications, Wellcome shall notify MGH and MGH may file such patent applications or maintain such patents at its own expense. Wellcome agrees to keep MGH informed of the prosecution of such patent applications, and unless MGH advises Wellcome or its designee that any action taken or proposed to be taken by Wellcome is improper within thirty (30) days of the forwarding of notice of such action or proposed action to MGH, Wellcome's action or proposed action shall be deemed to be correct.

MGH agrees to cooperate with Wellcome in filing and prosecuting such United States and foreign patent applications and in maintaining patents issued pursuant thereto and will cause its employees, agents and consultants, if any, to execute such documents as may in Wellcome's judgment be required in connection therewith.

ARTICLE XII. AUTHORIZATION UNDER DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT

MGH hereby authorizes Wellcome to exercise any rights that may be exercisable by MGH as patent owner under the Drug Price Competition and Patent Term Restoration Act of 1984 to apply for an extension of the term of any patent included within the Licensed Patents, as Wellcome in its discretion deems appropriate. MGH agrees to cooperate with Wellcome in the exercise of the authorization granted herein, and will execute such documents and take such additional action as Wellcome may reasonably request in connection therewith.

ARTICLE XIII. ASSIGNMENT

Neither party to this Agreement shall assign the same without the written consent of the other party; provided, however, that Wellcome, without such consent, may assign or sell the same in connection with the transfer or sale of all or substantially all of its business relating to human pharmaceuticals or in the event of its merger or consolidation with another company. Any permitted assignee shall assume all obligations of its assignor under this Agreement. No assignment shall relieve either party of responsibility for the performance of any accrued obligation which such party then has hereunder.

ARTICLE XIV. FORCE MAJEURE

The failure of either party to perform any term of this Agreement when caused by or resulting from fire, floods, embargoes, government regulations, prohibitions or interventions, war, acts of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts, acts of God, or any other cause beyond the control of such party, and which is a result thereof, shall not constitute a default or breach under any term of this Agreement.

ARTICLE XV. NOTICES

Any notice given under this Agreement shall be in writing and, unless otherwise provided for herein, shall be deemed to have been sufficiently given, when mailed by first-class mail, postage prepaid, addressed to the party to be notified at its address listed below or such other address as may be furnished in writing to the notifying party.

FOR WELLCOME:

Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709
Attn: Secretary

FOR MGH:

The General Hospital Corporation
55 Fruit Street
Boston, MA 02114
Attn: Director for
Research Administration

ARTICLE XVI. ENTIRE AGREEMENT; MODIFICATION

This Agreement contains the entire understanding of the parties with respect to the subject matter hereof. All express

or implied agreements and understandings, either oral or written, heretofore made are expressly merged in and made part of this Agreement. This Agreement may be modified only by a written instrument executed by both the parties hereto.

ARTICLE XVII. SEVERABILITY

Both parties hereby expressly agree and contract that it is the intention of neither party to violate any public policy, statutory or common laws, rules, regulations, treaty or decision of any government or agency thereof of any country or community or association of countries; that if any word, sentence, paragraph, clause or combination thereof of this Agreement is found, by a court or executive body with judicial powers having jurisdiction over this Agreement or any of the parties hereto, in a final unappealed or unappealable order, to be in violation of any such provisions in any country or community or association of countries, such words, sentences, paragraphs, clauses or combination shall be inoperative in such country or community or association of countries and the remainder of this Agreement shall remain binding upon the parties hereto.

ARTICLE XVIII. CONSTRUCTION AND GOVERNING LAW

The interpretation and construction of this Agreement shall be in accordance with the laws of North Carolina.

ARTICLE XIX. CAPTIONS

The captions to the several Articles hereof are not a part of this Agreement, but are merely guides or labels to assist in locating and reading the several Articles hereof.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be signed in duplicate by their respective authorized officers.

WITNESS:

Judith Gibian

THE GENERAL HOSPITAL CORPORATION

By: R. W. Lamont-Havers
Dr. R. W. Lamont-Havers

Its ~~Director, Research Policy and~~ Administration

WITNESS:

Paula Wilson

BURROUGHS WELLCOME CO.

By: Howard J. Schaeffer

Its Howard J. Schaeffer, Ph.D.
Vice President - Research, Development & Medical

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

March 20, 1992

The Commissioner of Patents
and Trademarks
Box AC for Patents
Washington, DC 20231

Attn: Office of the Assistant Commissioner for Patents
Gerald A. Dost, Special Programs Examiner

Dear Mr. Dost:

Pursuant to our conversation earlier today, I enclosed herewith a SUPPLEMENTAL DECLARATION for our APPLICATION FOR EXTENSION OF PATENT TERM for U.S. Patent No. 4,671,418. The SUPPLEMENTAL DECLARATION corrects the inadvertant omission from the original DECLARATION of paragraph 5), which omission you called to my attention today by telephone.

Thank you very must for your prompt initial review of our application and your timely contact.

Sincerely,

Lawrence A. Nielsen
(Reg. No. 29682)

enclosure

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 4,761,418
Issue Date: August 2, 1988
For: NOVEL COMPOUNDS
Inventors: Roy A. Swaringen, Jr., Hassan A. El-Sayad, David A. Yeowell; John A. Savarese
Assignee: Burroughs Wellcome Co.; General Hospital Corporation

SUPPLEMENTAL DECLARATION

To the Commissioner of Patents and Trademarks:

I, Lawrence A. Nielsen, residing at Chapel Hill, North Carolina, declare as follows:

1) That I am a patent agent authorized to practice before the United States Patent and Trademark Office and that my registration number is 29,682.

2) That I make this declaration as the agent of Burroughs Wellcome Co., a corporation of the State of North Carolina, having a place of business at 3030 Cornwallis Road, Research Triangle Park, North Carolina 27709 (hereinafter referred to as "Wellcome").

3) That United States Patent 4,761,418, issued August 2, 1988 (hereinafter referred to as the "Patent") is jointly assigned to Wellcome and General Hospital Corporation and that under the provisions of Article XII of the License Agreement between General Hospital Corporation and Wellcome, a redacted copy of which is attached herewith as EXHIBIT 3, Wellcome is authorized to apply for an extension of the term of the Patent on behalf of General Hospital Corporation.

4) That submitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156 of the Patent (hereinafter referred to as the "Application") on behalf of Wellcome requesting a 172 day extension of the term of the Patent.

5) That I have reviewed and understand the contents of the Application which is submitted pursuant to 35 U.S.C. 156.

6) That I believe that the Patent is subject to extension pursuant to 37 CFR 1.710.

7) That I believe that a 172 day extension of the term of the Patent is fully justified under 35 U.S.C. 156 and applicable regulations.

8) That I believe the Patent meets the conditions for the extension of the term of a patent as set forth in 37 CFR 1.720.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States patent 4,761,418, issued August 2, 1988, and any extensions thereof.

Lawrence A. Nielsen

Date: MARCH 20, 1992

Lawrence A. Nielsen
Reg. No. 29,682
Agent for Burroughs Wellcome Co.

Wellcome

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

TO: GERALD DOST

U.S PATENT AND TRADEMARK OFFICE

FROM: LARRY NIELSEN

NUMBER OF PAGES: 4 (including cover)

RE.: OUR FOLLOW-UP CONVERSATION EARLIER TODAY. THIS IS THE (CORRECTED) SUPPLEMENTAL DECLARATION FOR OUR APPLICATION FOR EXTENSION OF PATENT TERM FOR U.S. PATENT NO. 4,671,418. ~~SHOULD BE SIGNED THE ORIGINAL TO YOUR ATTENTION FOR PATENT EXTENSION~~ I WILL SEND THE ORIGINAL VIA EXPRESS MAIL TO YOUR ATTENTION. THANK YOU FOR YOUR HELP. THIS IS A RE-FAX. I FORGOT THE COVER LETTER.

PLEASE MAKE A NOTE OF OUR NEW FAX NUMBER: 919/248-0360

FACSIMILE/TELECOPIER:

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Patent Dept.

INFORMATION: 919-248-4219

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4,761,418

Burroughs Wellcome Co.

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Research Triangle Park, N.C. 27709

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March 20, 1992

The Commissioner of Patents
and Trademarks
Box AC for Patents
Washington, DC 20231

Attn: Office of the Assistant Commissioner for Patents
Gerald A. Dost, Special Programs Examiner

Dear Mr. Dost:

Pursuant to our conversation earlier today, I enclosed herewith a SUPPLEMENTAL DECLARATION for our APPLICATION FOR EXTENSION OF PATENT TERM for U.S. Patent No. 4,671,418. The SUPPLEMENTAL DECLARATION corrects the inadvertant omission from the original DECLARATION of paragraph 5), which omission you called to my attention today by telephone.

Thank you very must for your prompt initial review of our application and your timely contact.

Sincerely,

Lawrence A. Nielsen
(Reg. No. 29682)

enclosure

Docket No. 92/PD/436
"Express Mail" label no. AB192630427
Date of Deposit March 20, 1992

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Box AC for Patents,Washington, DC 20231.

Lawrence A. Nielsen
(Reg. No. 29682)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 4,761,418
Issue Date: August 2, 1988
For: NOVEL COMPOUNDS
Inventors: Roy A. Swaringen, Jr., Hassan A. El-Sayad, David A. Yeowell; John A. Savarese
Assignee: Burroughs Wellcome Co.; General Hospital Corporation

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